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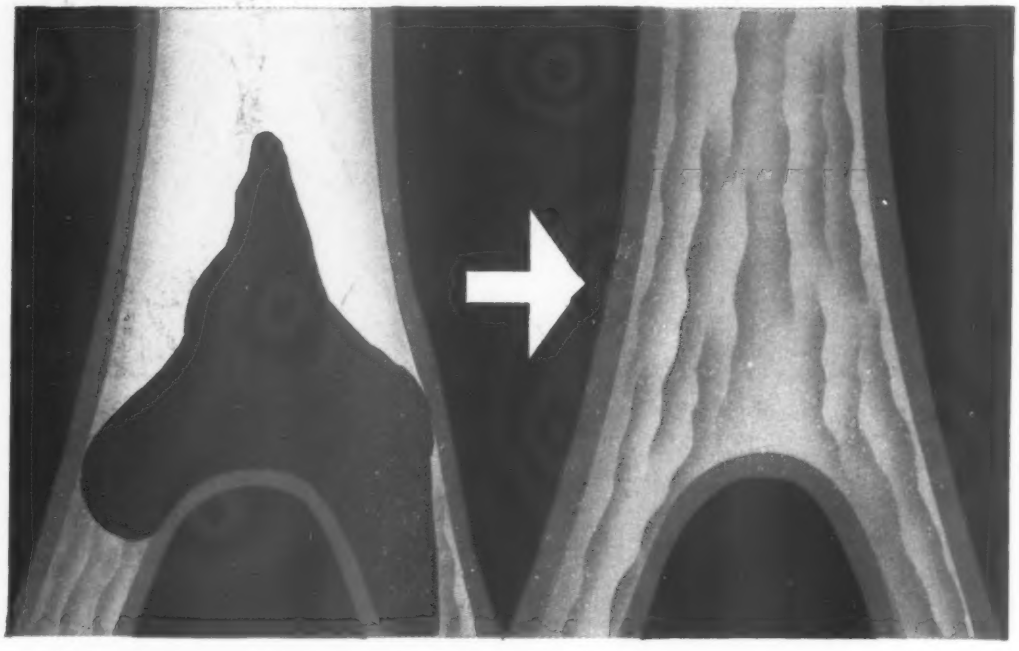

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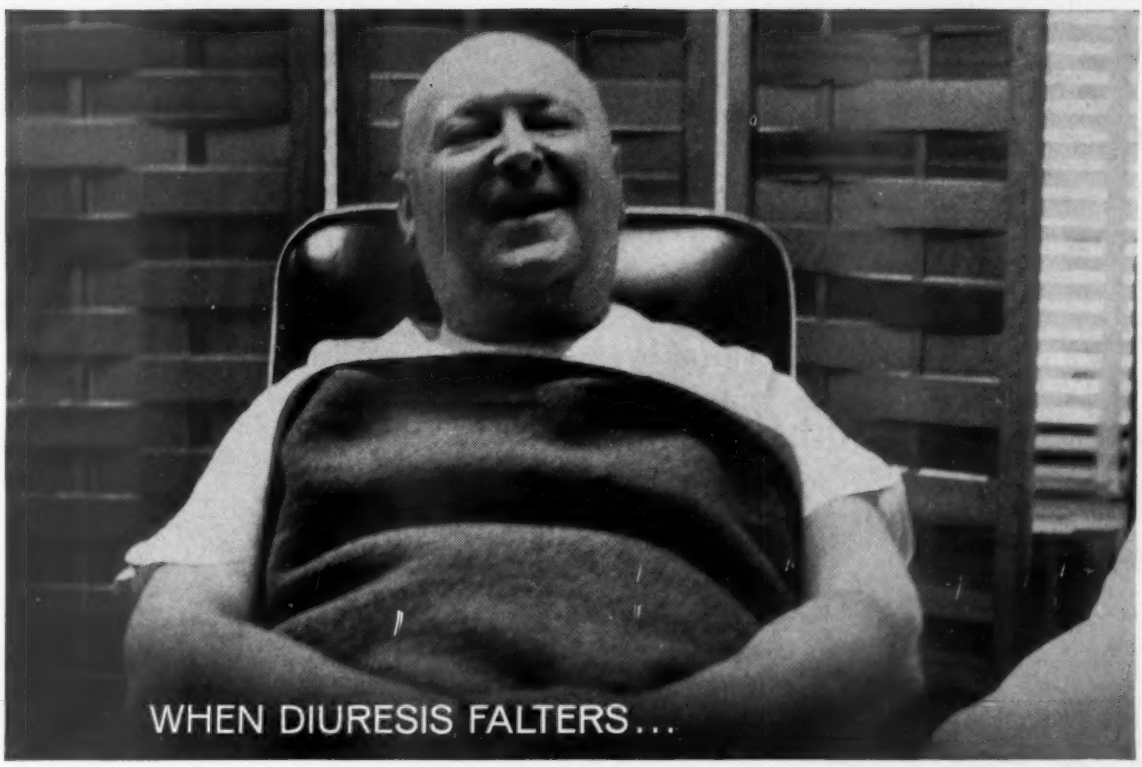

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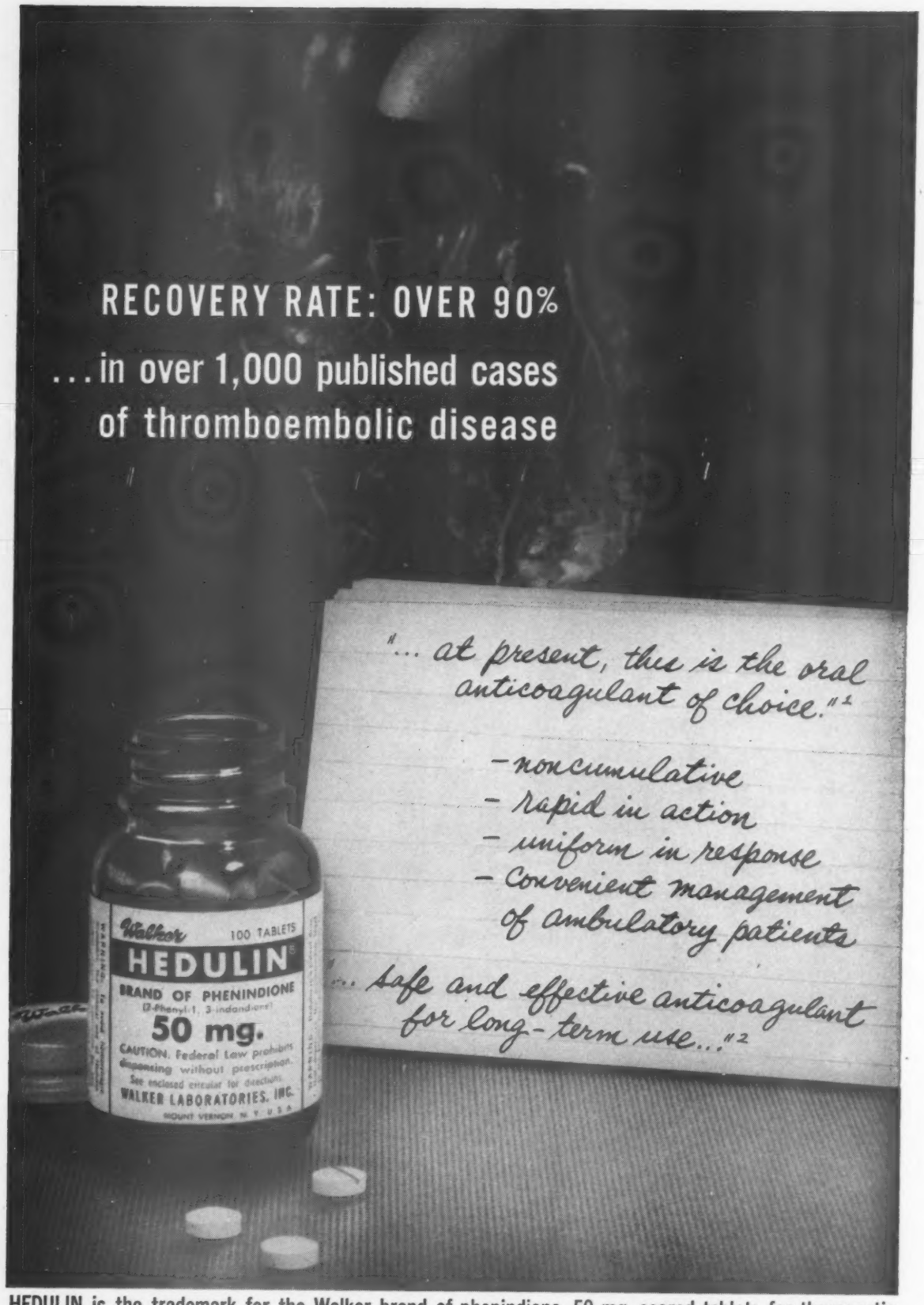
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1. Breneman, G. M., and Priest, E. McC.: Am. Heart J. 50:129 (July) 1955. 2. Tandowsky, R. M.: Am. J. Cardiol. 3:551 (April) 1959.

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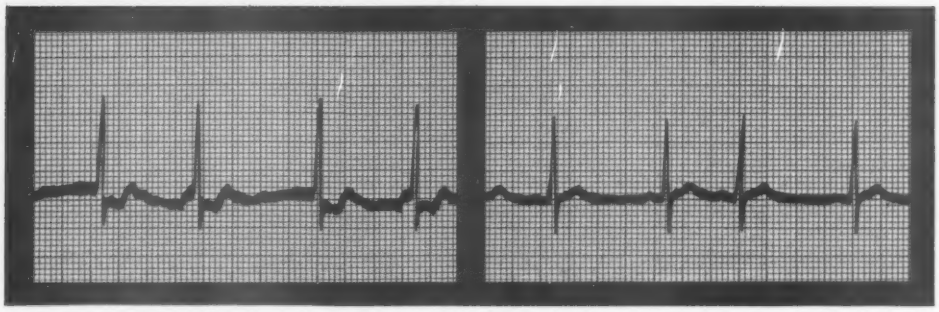

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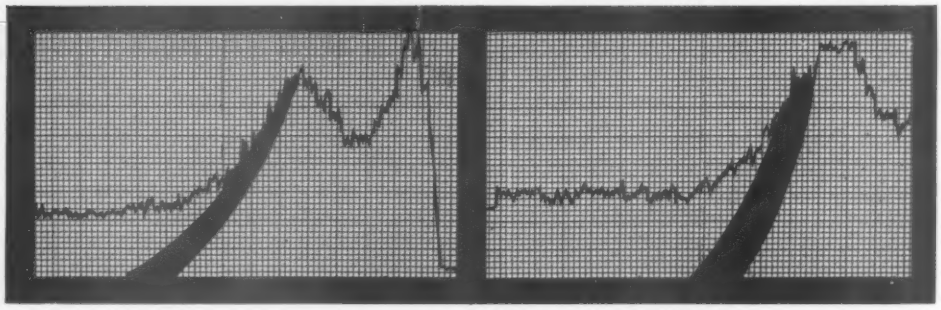

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Clinical Studies

Anatomic and Electrocardiographic Correlation of Fallot's Tetralogy. A Study of 100 Proved Cases 475
SHELDON R. BENDER, LEONARD S. DREIFUS AND DANIEL DOWNING

Frequently showing the pattern of right ventricular hypertrophy, the electrocardiogram in patients with tetralogy of Fallot neither lends itself to a specific anatomic diagnosis nor permits any correlation between right ventricular pressure and the height of R in V_1.

Right Ventricular Hypertrophy. Correlation of Electrocardiographic and Anatomic Findings 481
GONZALO T. ROMAN, JR., THOMAS J. WALSH AND EDWARD MASSIE

The best criteria for the electrocardiographic diagnosis of right ventricular hypertrophy are the following: (1) right axis deviation of ÂQRS (to the right of +110°); (2) R/S amplitude ratio in lead $V_1 > 1$ and (3) R/S amplitude ratio in lead V_6 = or <1.

The Normal QRS Vectorcardiogram in Infants and Children from Birth to Fifteen Years 488
HOMOBONO B. CALLEJA, RAYMOND E. BARKER AND RAY W. KISSANE

In the cube system of Grishman the horizontal projection is most informative concerning the QRS loop changes from birth to fifteen years. Normally, counterclockwise rotation should be seen at four months and the figure of eight pattern absent at ten years. At three months and over, the 0.03 second instantaneous vector should not be directed to the right.

The Vectorcardiogram in Direct Posterior Wall Myocardial Infarction 496
EDWIN L. ROTHFELD, ARTHUR BERNSTEIN, FRED W. WACHTEL AND WILLIAM S. KARLEN

A study of six patients with posterior wall infarctions shows the value of vectorcardiography in differentiating this condition from other causes of prominent R waves in the right precordial leads of electrocardiograms, such as right bundle branch block and right ventricular hypertrophy. In these vectorcardiograms the early forces of the QRS loop were abnormally displaced anteriorly and to the right.

The Vectorcardiogram in Dorsal or Posterior Myocardial Infarction 505
JOÃO TRANCHESI, VITOR TEIXEIRA, MUNIR EBAID, ITALO BOCCALANDRO, JOSÉ BOCANEGRA AND FÚLVIO PILEGGI

Counterclockwise rotation of QRSsÊ in the horizontal plane, the forward direction of these predominant forces and the orientation of TsÊ in the same direction facilitate the diagnosis of posterior infarction in cases in which a tall R wave in the right precordial leads might suggest right ventricular hypertrophy.

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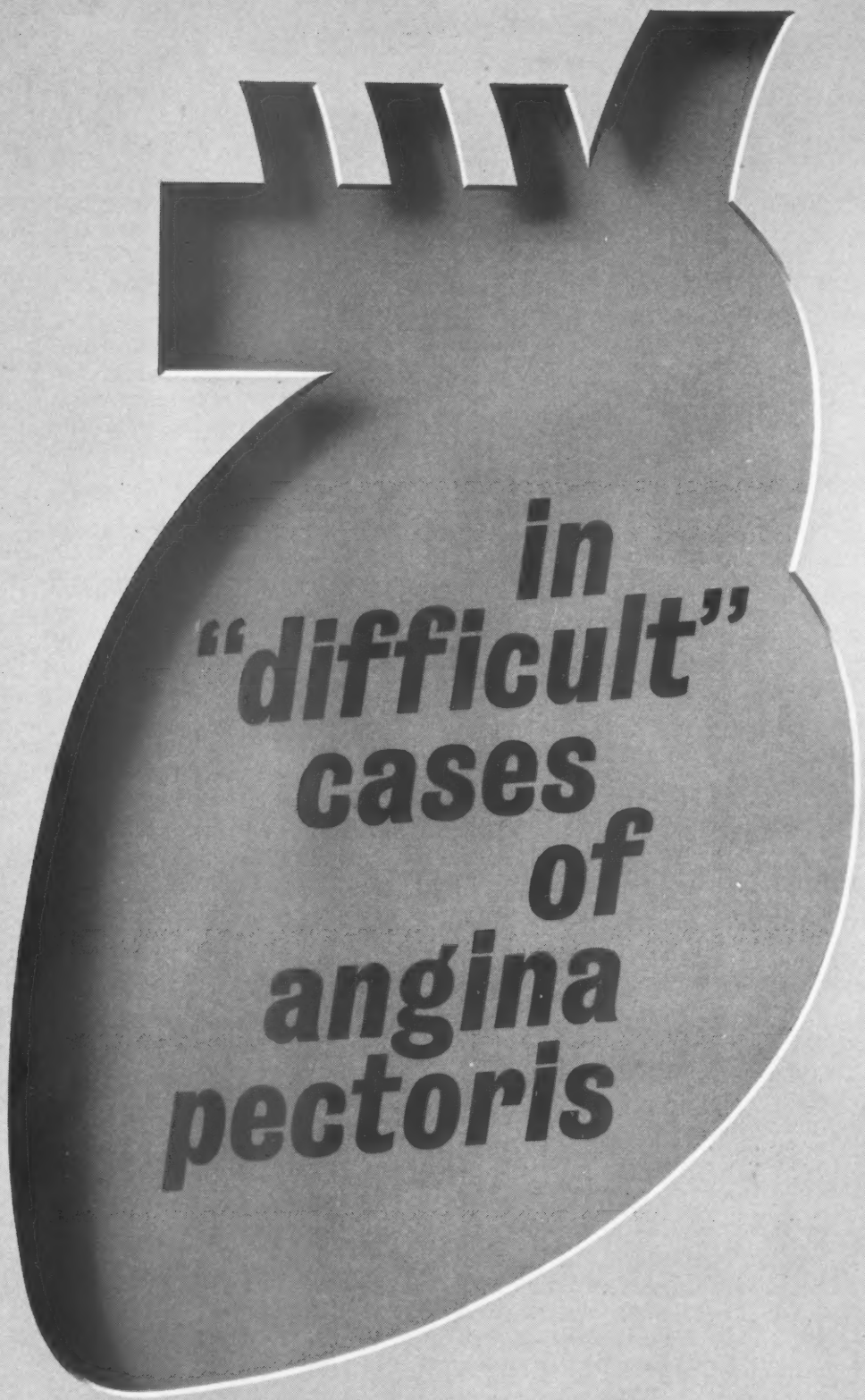

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ALI EKMEKCI, HIDEO TOYOSHIMA, JAN K. KWOCZYNSKI, TERUO NAGAYA AND MYRON PRINZMETAL

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MATTHEW J. FERGUSON

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Coronary angiography produced satisfactory diagnostic roentgenograms in fifty-two of sixty attempts and provided important data leading to surgical intervention in six patients. Rather unexpected was an apparently normal coronary tree in two patients with clinical angina.

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RICHARD GORLIN, NORMAN KRASNOW, HERBERT J. LEVINE, WILLIAM A. NEILL, RICHARD J. WAGMAN AND JOSEPH V. MESSER

In transseptal left heart catheterization, passage of the catheter over the puncturing needle directly into the left atrium can be accomplished without apparent hazard.

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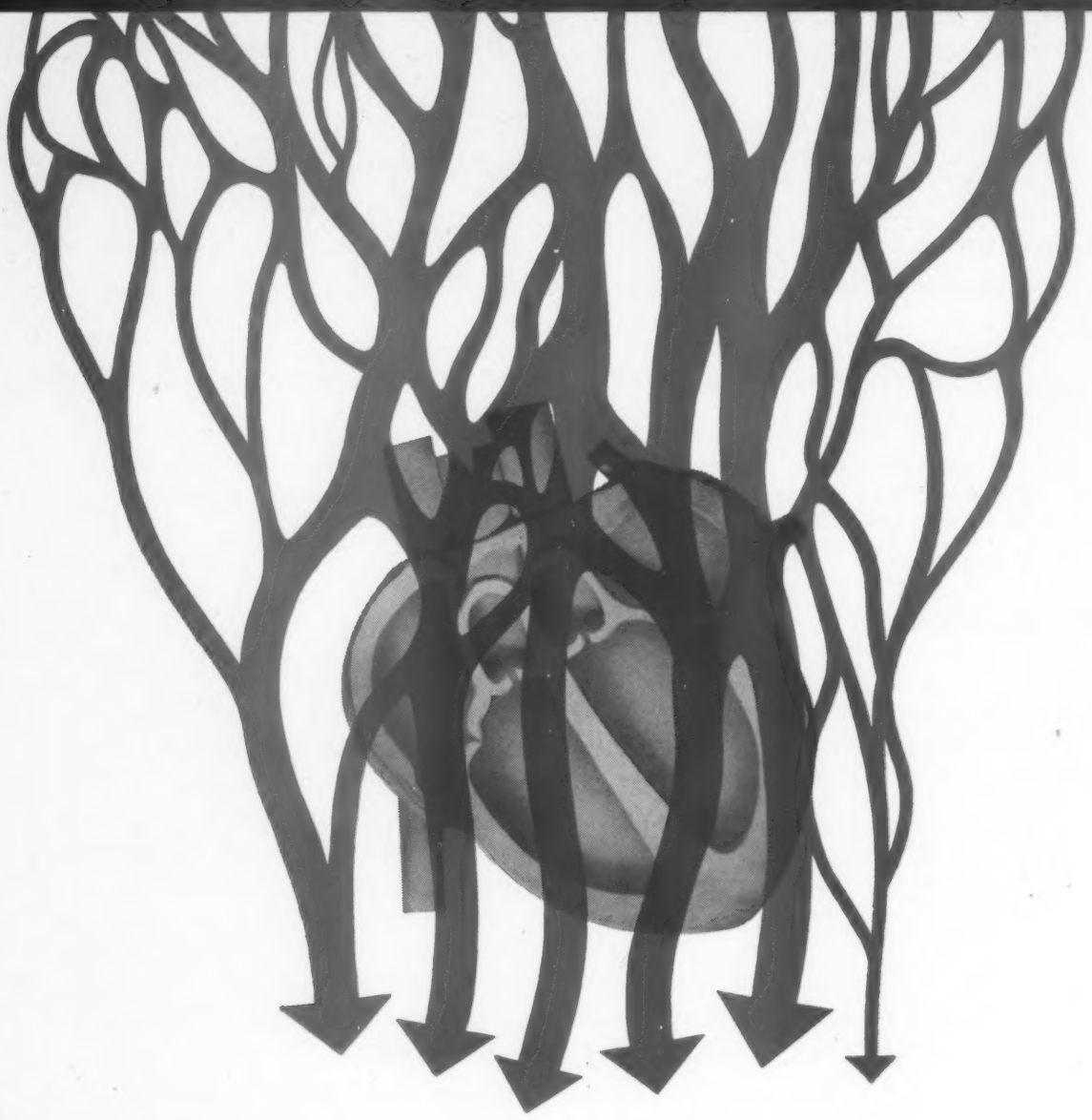

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Leslie, R.E.: Coronary Vasodilators—A Comparative Study (to be published)

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Fisch, S.; Boyle, A.; Sperber, R.; De Graff, A.C.: A Critical Review of Methods Used In Evaluating So-Called Coronary Vasodilators in Man, paper presented at the American Therapeutic Society Annual Meeting, Miami Beach, Florida, June 10, 1960.

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Evolution of Ventricular Septal Defect and Pulmonary Stenosis with Left to Right Shunt into Classic Tetralogy of Fallot. A Case Report with Clinical, Angiocardiographic and Anatomic Correlations 598
LUIS BECU, DANAE IKKOS, ARNE LJUNGQVIST AND ULF RUDHE

Subendocardial fibroelastic thickening of the moderately displaced crista supraventricularis is held responsible for the gradually increasing obstruction of the infundibulum of the right ventricle which produced a tetralogy of Fallot in an infant initially having clinical and roentgenologic signs of ventricular septal defect, a left to right shunt and moderate infundibular stenosis.

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HARRY NUSHAN, C. GLENN SAWYER, RICHARD O. ROGERS AND N. O'NEIL WHITLEY

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So that your article will be presented most effectively, illustrations must be glossy prints or professional drawings in black ink (never in blue; it will not reproduce well). Reference to all illustrations should be inserted in the text in consecutive order. Please follow these identification instructions: Write the figure number and the author's name on the back of each illustration and indicate the top.

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The American Journal of Cardiology

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Hygroton®
brand of chlorthalidone
in hypertension and edema, longer in action smoother in effect

Longer action[1] provides smooth, evenly-sustained therapeutic effect.[2] ■ Potent antihypertensive properties facilitate effective treatment of hypertension, frequently without auxiliary agents.[3] ■ Safeguards against significant potassium loss.[4] ■ Intensity of saluretic action enables liberalization of dietary salt restriction.[3] ■ Simplified dosage schedule affords economy of maintenance on just 3 doses per week.[2]

References: 1. Ford, R. V.: Current Therap. Research **2**:347, 1960. 2. Fuchs, M., and others: Current Therap. Research **2**:11, 1960. 3. Ford, R. V.: Connecticut Med. **24**:704-707, (Nov.) 1960. 4. Ford, R. V.: Texas State J. Med. **56**:343, 1960.

Detailed literature available on request.

Hygroton®, brand of chlorthalidone, is available as white, single-scored tablets of 100 mg.

Geigy Pharmaceuticals, Division of Geigy Chemical Corporation, Ardsley, New York HY573-61 **Geigy**

DRAMATIC
physical and emotional relief in
ANGINA PECTORIS

'round-the-clock protection against both pain and fear

COROVAS

Tymcaps

COROVAS is a nontoxic, uniform-acting, long-acting vasodilator to control or prevent attacks of angina pectoris. One COROVAS Tymcap upon arising provides up to 12 hours of continuous coronary vasodilation, and another COROVAS Tymcap before the evening meal affords maximum protection against seizures all night. COROVAS alleviates the associated fear of pain. Reduces the need for emergency nitroglycerin. Safe and effective for long-term therapy.

SUPPLIED—Boxes of 60 and 120.

PROLONGED, SUSTAINED ACTION OF VASODILATING PENTAERYTHRITOL TETRANITRATE (PETN) 30 MG., AND SEDATIVE SECOBARBITURIC ACID 50 MG. IN EACH COROVAS TYMCAP.
As with all nitrates, use with caution in glaucoma.

AMFRE GRANT, INC.
Brooklyn 26, N. Y.

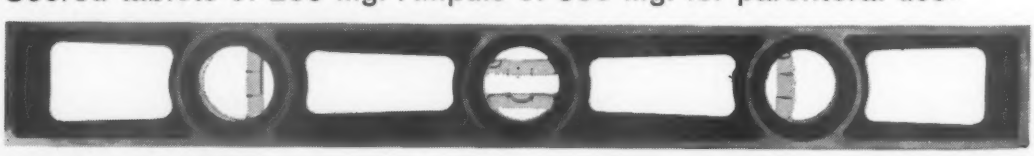
for balanced diuresis in:

cardiac edema • congestive heart failure • premenstrual tension • edema of pregnancy toxemia of pregnancy • obesity

often invaluable in: epilepsy Ménière's syndrome • glaucoma

Ample diuresis for the usual edematous patient . . . gentle . . . without excessive distortion of electrolyte or normal water patterns . . . without effect on blood pressure.

Scored tablets of 250 mg. Ampuls of 500 mg. for parenteral use.



DIAMOX®

Acetazolamide Lederle

LEDERLE LABORATORIES, a Division of AMERICAN CYANAMID COMPANY, Pearl River, New York

let's stop playing fast and loose with linoleic acid

There seems to be no doubt that *linoleic acid is the key factor* in dietary reduction of serum cholesterol. To reduce serum cholesterol, linoleic acid, the principal *poly*unsaturated fatty acid in edible vegetable fats, must *replace* some of the saturated and *mono*unsaturated fatty acids in the diet, not merely be added to the total intake.

This concept is clearly stated in the following quotation from a recent JAMA editorial: "It is accepted generally that specific alteration in the diet will lower the concentration of cholesterol in the blood. The most effective results to date have been achieved by increasing consumption of polyunsaturated fatty acids, particularly linoleic acid." "A particular regimen will be effective only if polyunsaturated fatty acids are responsible for an appreciable percentage of the total fat calories. That is, they must replace rather than supplement some of the saturated fats and oils already in the diet."[1]

In spite of this clear and unbiased statement, the advertising of some margarines seems designed to mislead physicians and their patients by capitalizing on the publicity given to corn oil as the principal source of linoleic acid. The following ambiguous claims are typical:

According to the headline:

The margarine is made of 100% Corn Oil. Buried in the body copy are the words partially hydrogenated.

Misleading because:

The partial hydrogenation has largely converted linoleic acid into saturated fats and into monounsaturated oleic acid, which has been observed to have no effect on serum cholesterol.

According to the headline:

Some claim to have twice the corn oil nutritional benefit of any other leading spread.

Misleading because:

Such a statement obviously implies that this margarine has twice as much linoleic acid, hence greater cholesterol-lowering effect. The truth is that you can buy a margarine with significantly higher linoleic acid content in drugstores.

And so it goes. Literature sent to physicians and journal ads to the profession have been equally misleading. For example, *references being cited refer to clinical studies with a totally different product.* No wonder the author of the editorial cited above felt compelled to warn physicians about "widespread misinformation in this field!"

We don't like such misleading advertising, and we don't use it to promote Emdee Margarine. We're content to deal in facts:

- **Emdee Margarine contains significantly more linoleic acid than other corn oil margarines currently marketed—and contains significantly less of the unnatural trans isomer forms of fatty acids.**
- **Emdee Margarine—and only Emdee Margarine—was used in clinical evaluation studies, even though others now cite the references.**
- **Emdee Margarine—and only Emdee Margarine—has published reports of its value in cholesterol-lowering diets, including articles in JAMA[2], Geriatrics[3], and American Journal of Clinical Nutrition[4].**

Corn oil margarines are *not* alike. They vary greatly in percentage of the active ingredient—linoleic acid. Of them all, Emdee Margarine has far more linoleic acid. It's true that our patented linoleic acid-sparing process makes Emdee Margarine more expensive. But, it's *worth more* when you want your patient's serum cholesterol to go down.

Although the misleading promotion of some margarines may confuse some of your patients, we feel certain that it will not deceive the critical physician —and that you will continue to depend, as you always have, on the facts and on your own clinical evaluation of your patient's needs.

PITMAN-MOORE COMPANY
DIVISION OF ALLIED LABORATORIES, INC., INDIANAPOLIS 6, INDIANA

EMDEE®
margarine

References: 1. Pollack, H.: J.A.M.A. *172*:1165 (Mar. 12) 1960. 2. Boyer, P. A.; Lowe, J. G.; Gardier, R. W., and Ralston, J. D.: J.A.M.A. *170*:257 (May 16) 1959. 3. Terman, L. A.: Geriatrics *14*:111 (Feb.) 1959. 4. Jolliffe, N.; Rinzler, S. H., and Archer, M.: Am. J. Clin. Nutrition *7*:451 (July-Aug.) 1959.

special process protected by
U. S. Patent No. 2,890,959

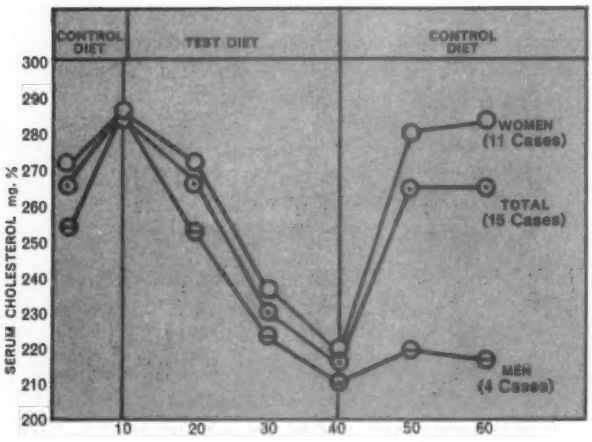
(SEE OTHER SIDE FOR ADDITIONAL INFORMATION ON EMDEE MARGARINE)

Corn oil margarines are *not* alike in linoleic acid content and, therefore cannot all be of equal value in lowering serum cholesterol. Emdee Margarine contains *significantly more linoleic acid* than any other corn oil margarine currently marketed. Emdee Margarine is the *only* margarine with published scientific reports of its value in reducing serum cholesterol.

Serum cholesterol goes down

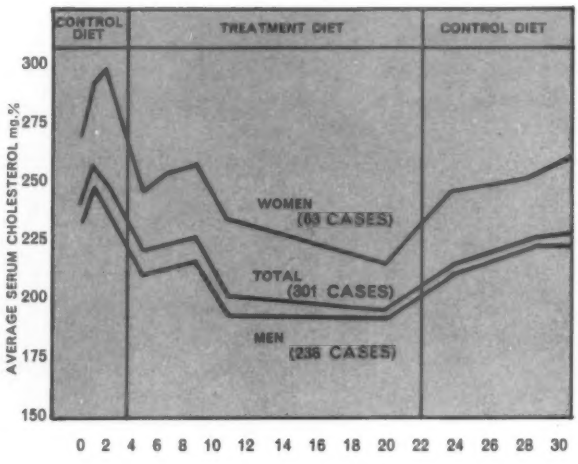
when Emdee Margarine is substituted for spreads and shortenings containing more saturated or hydrogenated fatty acids.

Emdee Margarine in place of other spreads and shortenings has been shown to be a practical way to lower serum cholesterol without complicating or creating a weight reduction problem. Emdee provides effective levels of linoleic acid. In clinical studies, patients accepted Emdee Margarine without reservation. Results of these studies indicate Emdee's effectiveness:



TIME IN DAYS

"Average serum cholesterol values were noticeably reduced during the test diet, becoming statistically significant at the end of the second ten-day period and showing increasing significance at the end of the third ten-day period."[1]



TIME IN WEEKS

"In a nine-month study of over 300 inpatients in a state institution, it was found that a regimen employing a nonhydrogenated corn oil margarine (Emdee Margarine) for other solid fats as the principal dietary alteration was effective in achieving and maintaining a reduction in blood cholesterol levels."[2]

References: 1. Terman, L. A.: Geriatrics *14*:111 (Feb.) 1959. 2. Boyer, P. A.; Lowe, J. G.; Gardier, R. W., and Ralston, J. D.: J.A.M.A. *170*:257 (May 16) 1959.

When You Want to Lower Blood Cholesterol

EMDEE®
margarine

PITMAN-MOORE COMPANY
DIVISION OF ALLIED LABORATORIES, INC., INDIANAPOLIS 6, INDIANA

To protect flavor and texture, Emdee Margarine is packaged in cans and kept under constant refrigeration. The linoleic acid-sparing manufacturing process is covered by U. S. Patent No. 2,890,959.

Schering

for your patient with

hypertension

these benefits from

Naqua™

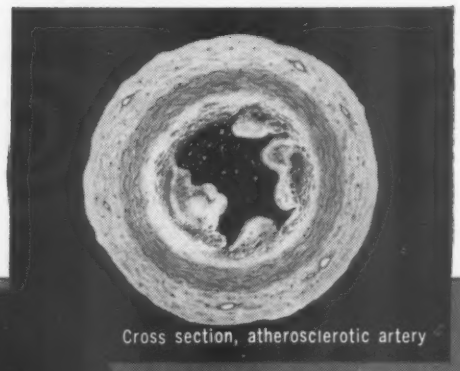
trichlormethiazide

often the only drug required for satisfactory reduction of blood pressure in both mild and moderate hypertension...commonly relieves headache, palpitation, etc.[1]...may further reduce blood pressure levels reached on previous regimens[2]...usually obviates need for potassium supplements...potentiates effect of some adjunctive antihypertensive agents, decreasing their dosage needs, thereby reducing their potential side effects...economically priced for special benefit of long-term patients. **Packaging:** NAQUA Tablets, 2 and 4 mg., scored, bottles of 100 and 1000.

References: (1) Cohen, B. M.: Newer Saluretic Agents in the Therapy of Hypertension, paper presented at 6th Internat. Cong. Int. Med., Basel, Switzerland, Aug. 24-27, 1960. (2) Ford, R. V.: Am. J. Cardiol. **5**:407, 1960.

S-722

outstanding nutritional research achievement



Cross section, atherosclerotic artery

to aid in the dietary control of serum cholesterol

MAZOLA®

MARGARINE
scientifically formulated with pure liquid non-hydrogenated MAZOLA Corn Oil.

U.S. Pat. No. 2,955,039

MAZOLA Margarine is an economical tablespread and serves as a solid shortening, rich in linoleates and low in saturates—making it an ideal dietary adjunct in the management of serum cholesterol. It contains 2 to 3 times as much natural linoleic acid as any other margarine readily available in grocery stores from coast to coast, and 5 to 8 times as much as butter. It contains no dairy or animal fats, no coconut oil, and no cholesterol.

MAZOLA Margarine is indistinguishable from other quality margarines as to taste, aroma and handling characteristics. Thus, it can be part of the regular diet for the whole family, including the hypercholesterolemic patient. The major ingredient in MAZOLA Margarine—liquid MAZOLA Corn Oil—is NOT hydrogenated, thereby preserving its rich content of linoleates.

The average daily intake, two ounces or 56.8 Gm. (4 tablespoons) of MAZOLA Margarine, supplies

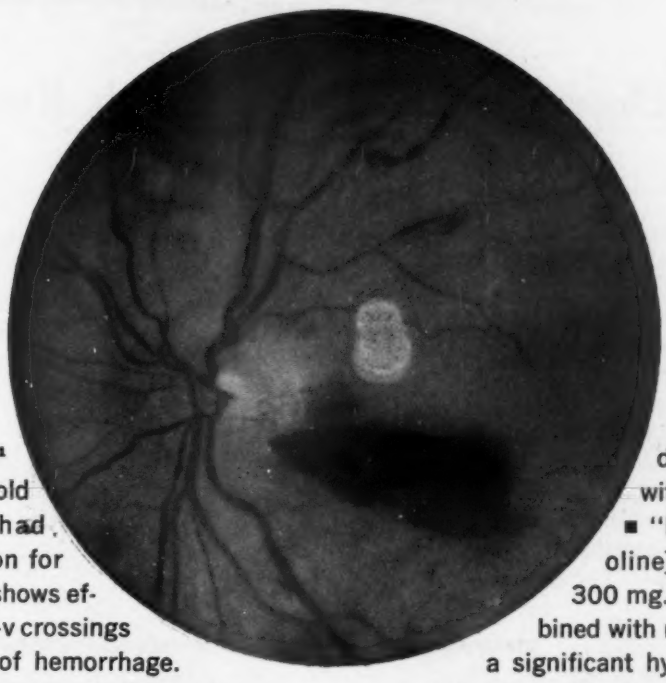
Linoleic acid	12 Gm.
Oleic acid	23 Gm.
Saturated fatty acids	8 Gm.
Plant sterols (sitosterols)	215 mg.
Natural tocopherols	30 mg.
Vitamin A	1870 USP units
Vitamin D	250 USP units
Calories	415

Available in the refrigerator sections of grocery stores in the same general price range as other premium quality margarines, in 1-lb. packages (four ¼ lb. sticks).

Send for free booklet:
"Recent Advances in the Dietary Control of Hypercholesterolemia."

BEST FOODS • Division of Corn Products Co., NEW YORK 22, N. Y.

When blood pressure must come down



AS IN THIS CASE:[1] Fundus of 62-year-old female who has had severe hypertension for many years. Photo shows effect of pressure at a-v crossings and various types of hemorrhage.

■ When you see eyeground changes like this—with such hypertensive symptoms as dizziness and headache—your patient is a candidate for Serpasil-Apresoline. With this combination the antihypertensive action of Serpasil complements that of Apresoline to bring blood pressure down to near-normal levels in many cases. Side effects can be reduced to a minimum, since Apresoline is effective in lower dosage when given with Serpasil.

■ "Hydralazine [Apresoline] in daily doses of 300 mg. or less, when combined with reserpine, produced a significant hypotensive effect in a large majority of our patients with fixed hypertension of over three years' duration."[2]

Complete information sent on request.

SUPPLIED: Tablets #2 (standard-strength), each containing 0.2 mg. Serpasil and 50 mg. Apresoline hydrochloride. **Tablets #1** (half-strength), each containing 0.1 mg. Serpasil and 25 mg. Apresoline hydrochloride. /2832 HK

1. Bedell, A. J.: Clin. Symposia 9:135 (Sept.-Oct.) 1957.
2. Lee, R. E., Seligman, A. M., Goebel, D., Fulton, L. A., and Clark, M. A.: Ann. Int. Med. 44:456 (March) 1956.

Serpasil®-Apresoline®

hydrochloride

(reserpine and hydralazine hydrochloride CIBA)

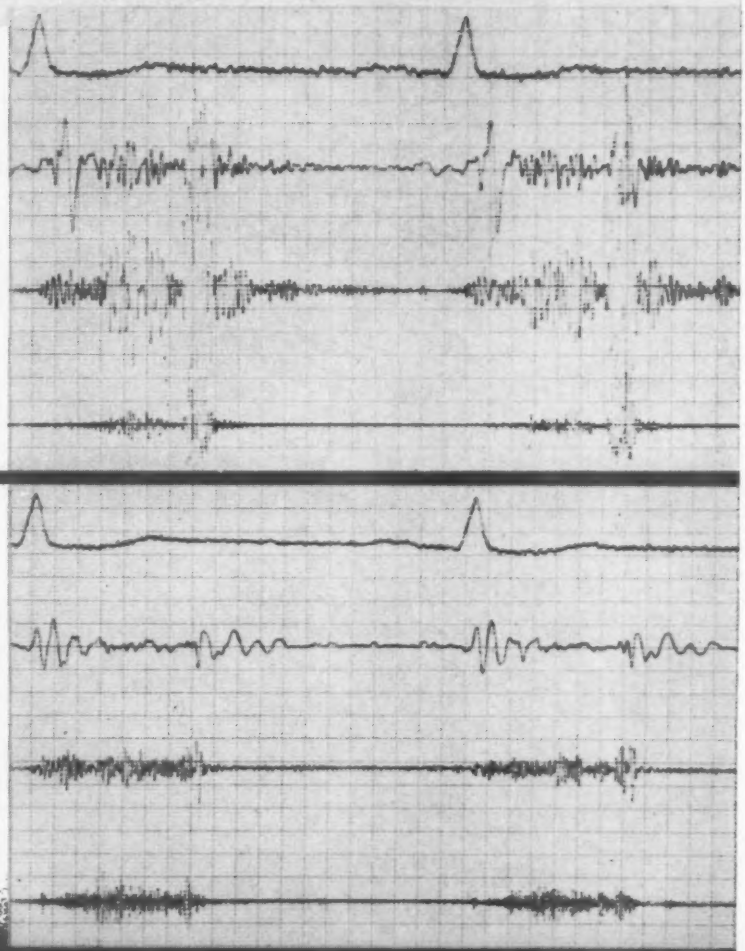
CIBA
SUMMIT, N. J.

PHONOCARDIOGRAPHY

with the Direct Jet-Writing

Elema-Schönander Mingograph Recorders

Two, three and four-channel units permitting common base line and overlapping curve recordings. Each channel equipped with AC and DC input for recordings of all physiological phenomena. Direct and accurate recordings of all frequencies up to 900 C/S. Simple controls assure easy operation.
Six paper speeds.
Low cost paper.



★ *At Right are actual recordings made with the Mingograph, model 42B, showing one EKG lead and three phonocardiographic curves, each taken through a different filter.*

Available through your local X-Ray dealers.

DISTRIBUTORS FOR THE UNITED STATES:

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Proven

in over six years of clinical use and
more than 750 published clinical studies

Effective

for relief of anxiety and tension

Outstandingly Safe

1. simple dosage schedule produces rapid, dependable tranquilization without unpredictable excitation
2. no cumulative effects, thus no need for difficult dosage readjustments
3. does not produce ataxia, change in appetite or libido
4. does not produce depression, Parkinson-like symptoms, jaundice or agranulocytosis
5. does not impair mental efficiency or normal behavior

Miltown®

meprobamate (Wallace)

Usual dosage: One or two 400 mg. tablets t.i.d.
Supplied: 400 mg. scored tablets, 200 mg. sugar-coated tablets; in bottles of 50.

Also supplied in sustained-release capsules . . .

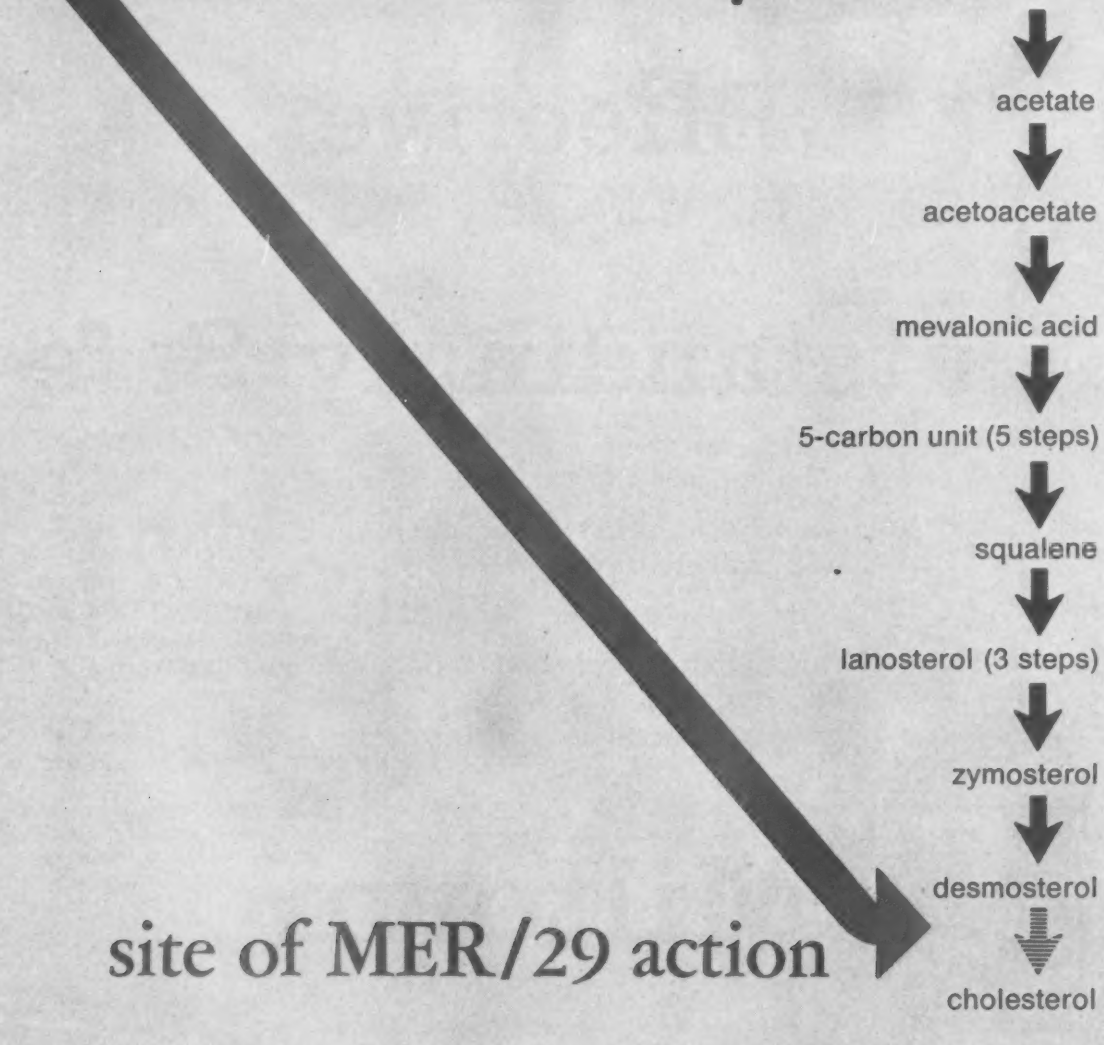
Meprospan®

Available as Meprospan-400 (blue-topped *sustained-release* capsules containing 400 mg. meprobamate), and Meprospan-200 (yellow-topped *sustained-release* capsules containing 200 mg. meprobamate).

CM-4234

WALLACE LABORATORIES / *Cranbury, N. J.*

specific[1], demonstrated[2] inhibition[3] of cholesterol biosynthesis...



1. The primary, the *only* known action of MER/29 is to lower the total body pool of sterols (serum and tissue); no effect on any other system or organ reported to date.

2. "Using each patient as his own control, the peak *total* sterol radioactivity after injection of mevalonic acid-2-C^{14} was compared on and off MER/29. As much as a 50 per cent inhibition on MER/29 was observed in some patients."
—Steinberg, D.; Avigan, J., and Feigelson, E. B.: Circulation *22*:663 (Oct.) 1960.

3. "Studies of lipid metabolism have stressed the importance of cholesterol biosynthesis, as opposed to cholesterol intake, in determining cholesterol balance."
—National Heart Institute: Diet, Hormones, and Atherosclerosis..., Bethesda, Md., U.S. National Institutes of Health, 1958.

...leading to specific, demonstrated advantages in cholesterol-lowering therapy

particularly in patients with coronary artery disease, generalized atherosclerosis, and other conditions thought to be associated with abnormal cholesterol metabolism

MER/29 REDUCES CHOLESTEROL IN AS MANY AS 8 OUT OF 10 PATIENTS: MER/29 reduces both serum and tissue cholesterol without strict adherence to diet. Although some physicians prefer to use MER/29 in conjunction with controlled diets, cholesterol can be reduced successfully without such limitation.

CONCURRENT BENEFITS REPORTED IN SOME PATIENTS: In patients with coronary artery disease, some of the concurrent benefits reported include decreased incidence and severity of anginal attacks, improved ECG patterns, diminished nitroglycerin dependence, and increased sense of well-being.

MER/29 HAS PRODUCED FEW SIDE EFFECTS, NO TOXICITY: Patients have been treated with MER/29 for continuous periods up to 19 months. In no case has there been evidence of serious toxic effects on the function of any vital organ or system. Side effects (nausea, headache, dermatitis) are rare and have usually been associated with dosages greater than those recommended for effective therapy.

MER/29 is compatible with other cardiovascular therapies. It can be used along with measures which control anxiety, hypertension, obesity and other conditions associated with cardiovascular disorders. These include nitroglycerin, PETN, and anticoagulants.

CAUTION: Since long-term MER/29 therapy may be necessary, periodic examinations, including liver function tests, are desirable. Also, since MER/29 inhibits cholesterol biosynthesis, and cholesterol plays an important role in the development of the fetus, the drug is *contraindicated in pregnancy.*

DOSAGE: One 250 mg. capsule daily, before breakfast.

SUPPLIED: Bottles of 30 pearl gray capsules.
Complete bibliography and product information available on request.

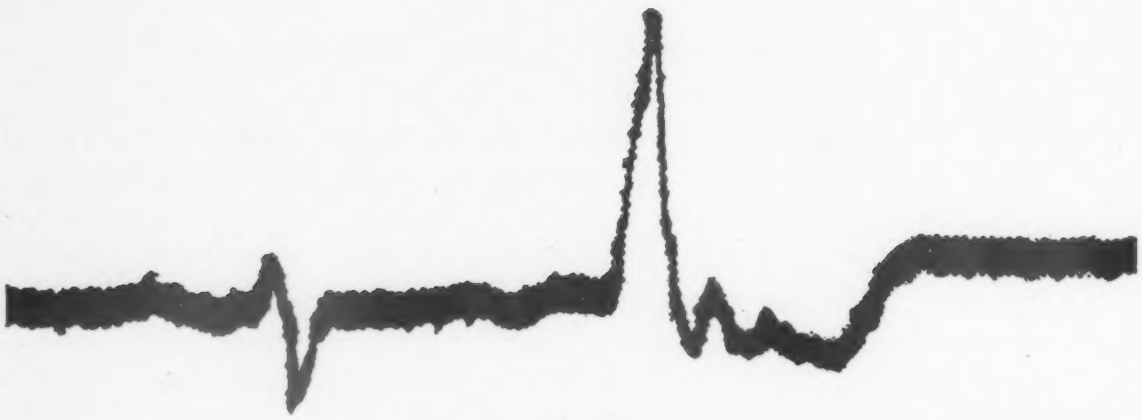
MER/29

(triparanol)

Merrell
SINCE 1828

The Wm. S. Merrell Company
Division of Richardson-Merrell Inc.
Cincinnati, Ohio • Weston, Ontario

Trademark: MER/29®



for cardiac arrhythmias... obvious advantages

PRONESTYL® HYDROCHLORIDE

SQUIBB PROCAINE AMIDE HYDROCHLORIDE

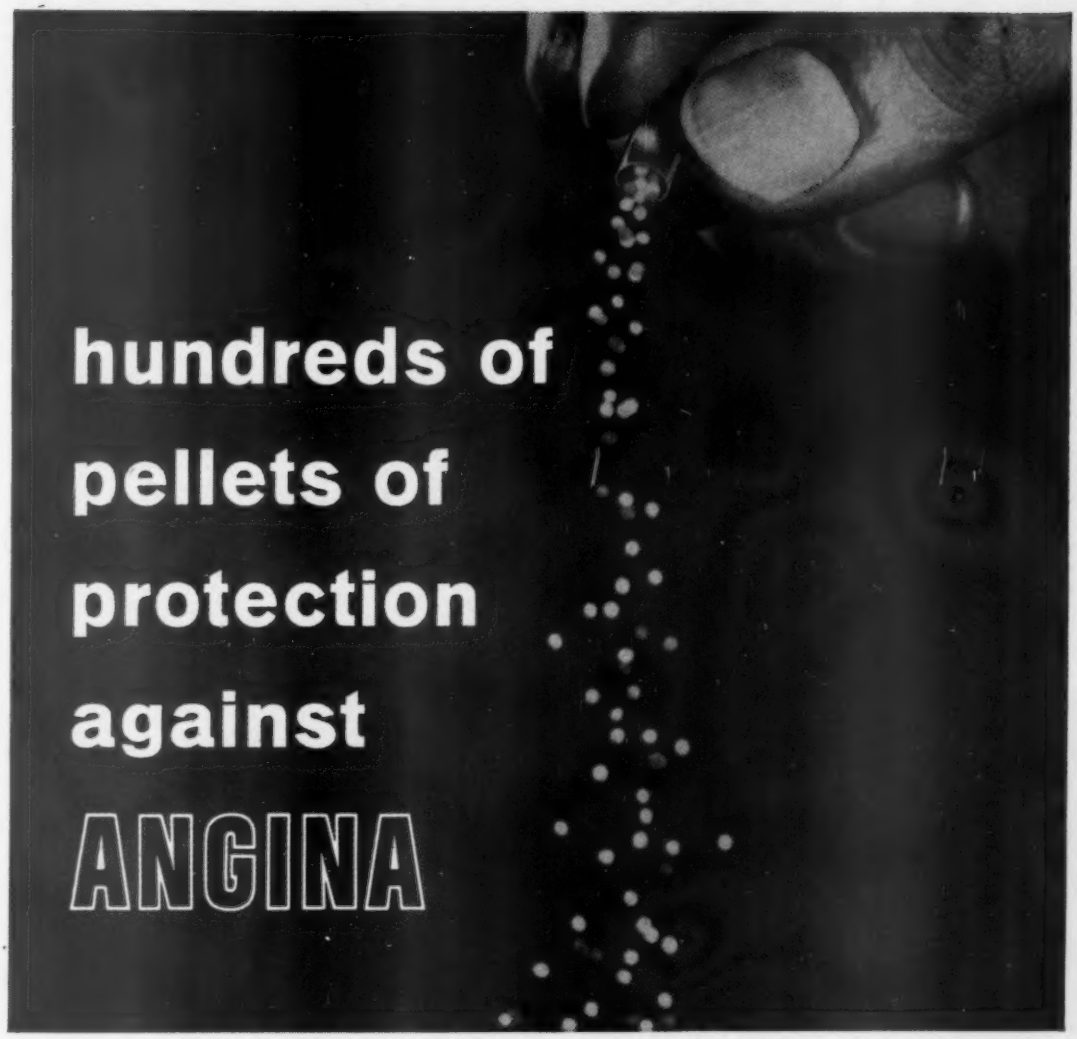
Pronestyl offers obvious advantages over quinidine and procaine in the management of cardiac arrhythmias: Procaine amide [Pronestyl] should be a "drug of choice in arrhythmias of ventricular origin." [1]—administered I.V., Pronestyl is better tolerated than a corresponding I.V. dose of quinidine—administered I.M., Pronestyl acts faster than I. M. quinidine[2]—Pronestyl sometimes stops arrhythmias which have not responded to quinidine[3,4]—Pronestyl may be used in patients sensitive to quinidine—more prolonged action, less toxicity, less hypotensive effect than procaine—no CNS stimulation such as procaine may produce.

Supply: For convenient oral administration: Capsules, 0.25 gm., in bottles of 100.
For I. M. and I. V. administration: Parenteral Solution, 100 mg. per cc., in vials of 10 cc.

References: 1. Zapata-Diaz, J., et al.: Am. Heart J. 43:854, 1952. 2. Modell, W.: In Drugs of Choice, C.V. Mosby Co., St. Louis, 1958, p. 454. 3. Kayden, H. J., et al.: Mod. Concepts Cardiovasc. Dis. 20:100. 1951. 4. Miller, H., et al.: J.A.M.A. 146:1004, 1951.

SQUIBB *Squibb Quality—the Priceless Ingredient*

'PRONESTYL'® IS A SQUIBB TRADEMARK



PENTRITOL® TEMPULES

controlled disintegration capsules

A single 30 mg. Pentritol Tempule with 12 hour action exhibits an even nitrite release which "tends to produce a smooth, prolonged response similar to that of the sustained release of modern depot injections."[1] Duration, frequency, and severity of anginal attacks are markedly lessened. Patients showing little progress during years of therapy with 80 mg. daily of PETN tablets, respond favorably to the smaller dose of Pentritol Tempules.[2] Kamil and Klinger report the response of their patients to a timed-disintegration pentaerythritol tetranitrate capsule as excellent, with nitroglycerin requirements reduced as much as 85%.[3]

1. Biegeleisen, H. I.: Clin. Med. *2*:1005, 1955. 2. Roberts, J. T.: Clin. Med. *4*:1375, 1957. 3. Kamil, M., and Klinger, I.: New York State J. Med. *59*:3398, 1959.

PENTRITOL

Each Pentritol Tempule is a controlled disintegration capsule containing 30 mg. of pentaerythritol tetranitrate in granular form. An initial dose of 10 mg. is released at once; a second dose 4 hours later; and a third dose 8 hours after ingestion. Thus, each Tempule affords at least 12 hours of coronary vasodilation. ACTION AND USES: Effective therapy for and prophylaxis against anginal attacks. One Tempule morning and evening will provide 24 hours of effective medication, with a smooth, sustained clinical effect that has shown superior results. Pentritol reduces or eliminates nitroglycerin requirements, stops or reduces frequency of anginal attacks, eliminates or mitigates pain, and increases capacity for physical activity. CONTRAINDICATIONS: Observe caution in glaucoma. DOSAGE: One Pentritol Tempule morning and evening, approximately 12 hours apart. SUPPLIED: Bottles of 60 and 250. Also available: Pentritol®-B Tempules®, with 30 mg. pentaerythritol tetranitrate and 50 mg. butabarbital, for 12 hours of coronary vasodilation plus sedation.

ARMOUR PHARMACEUTICAL COMPANY
KANKAKEE, ILLINOIS • *Armour Means Protection*

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oral aminophylline

readily tolerated

by almost every patient

AMINOPHYLLINE DURA-TAB S.M.®

Oral Sustained Medication* Aminophylline 4½ gr. (.3 Gm.)

one dose q.12 h. maintains effective uniform blood levels in cardio-pulmonary conditions

Many patients who cannot tolerate ordinary aminophylline tablets can now take **Aminophylline Dura-Tab S.M.** without gastric irritation. The reason: only a fraction of this sustained-action aminophylline contacts the gastric membranes—the balance being absorbed slowly all along the intestinal tract.

one dose q. 12 h. (1 to 2 Aminophylline Dura-Tabs) in adults maintains effective blood levels. For children under 10, one-half Dura-Tab q. 8 to 10 h. • Indicated in bronchial asthma, pulmonary emphysema, congestive heart failure, angina pectoris, paroxysmal dyspnea and Cheyne-Stokes respiration.

Bottles of 30, 100, 250—cost comparable to ordinary aminophylline tablets.

*U. S. Patent No. 2,895,881

Samples and literature upon request.

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FOR ORAL, INTRAVENOUS OR INTRAMUSCULAR USE

the proven anticoagulant for long-term maintenance

now more widely prescribed than all other oral anticoagulants combined

152,000,000

Over ~~131,000,000~~ doses administered to date

Over 125 published papers since 1953

Endo®

the original and only warfarin responsible for establishing this drug as closely approaching the ideal anticoagulant.[1,2]

1. Baer, S., et al.: J.A.M.A. 167:704, June 7, 1958.
2. Moser, K. M.: Disease-a-Month, Chicago, Yr. Bk. Pub., Mar., 1960, p. 13.

Full range of oral and parenteral dosage forms— COUMADIN* (warfarin sodium) is available as: Scored tablets—2 mg., lavender; 5 mg., peach; 7½ mg., yellow; 10 mg., white; 25 mg., red. Single injection units—one vial, 50 mg., and one 5 cc. ampul Water for Injection; one vial, 75 mg., and one 3 cc. ampul Water for Injection.

Average Dose: Initial, 40-60 mg. For elderly and/or debilitated patients, 20-30 mg. Maintenance, 5-10 mg. daily, or as indicated by prothrombin time determinations.

*Manufactured under license from the Wisconsin Alumni Research Foundation.

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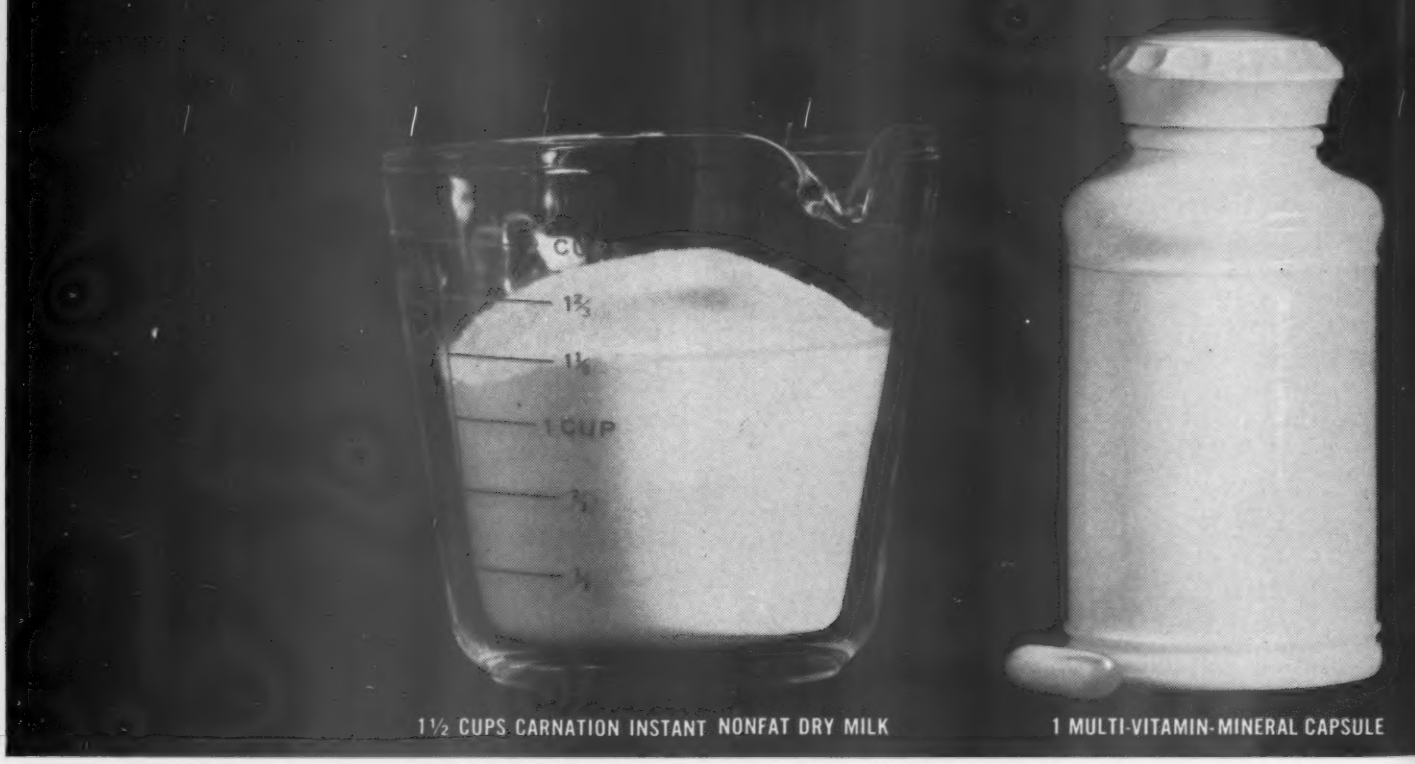
ENDO LABORATORIES Richmond Hill 18, New York

ANNOUNCING: THE CARNATION WEIGHT REDUCTION PLAN

AN EFFECTIVE MEAL-REPLACEMENT FORMULA DIETING PATIENTS CAN MAKE AT HOME—FOR ONLY 44¢ A DAY



1½ CUPS CARNATION INSTANT NONFAT DRY MILK

1 MULTI-VITAMIN-MINERAL CAPSULE

THE CARNATION WEIGHT REDUCTION PLAN

This Plan is a *new* meal-replacement weight reduction regimen based on delicious milk products plus a standard multi-vitamin-mineral preparation.

Carnation's nutritionally-balanced meal-replacement Plan supplies 1000 calories and 70 grams of high quality protein.

EASY FOR PATIENTS TO MAKE

TAKE 1 standard multi-vitamin-mineral preparation each day.

MIX one day's supply (4 glassfuls) of Carnation Plan Formula by stirring together in a container larger than a quart:

1½ cups CARNATION INSTANT NONFAT DRY MILK

1 quart WHOLE MILK

If desired, flavor with instant coffee or a variety of extracts.

Chocolate flavoring adds 30 calories per teaspoonful.

OR for a Single Glass: Mix a generous ⅓ cup Carnation Instant with 1 cup whole milk.

COSTS ONLY 44¢ A DAY

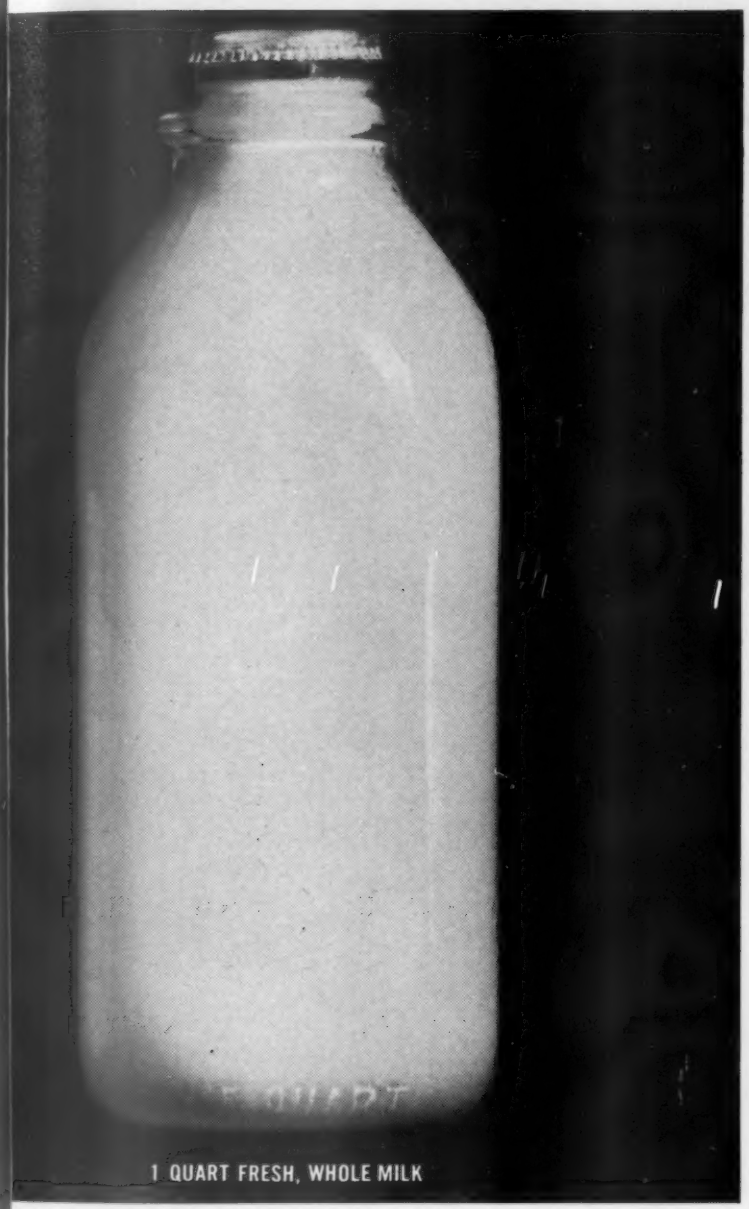
The total expense for the Carnation Weight Reduction Plan —including the multi-vitamin-mineral preparation—is 44¢ a day. Compare this to the price dieters pay for the largest-selling pre-mixed product.

TASTES NATURALLY DELICIOUS

Because the Carnation Plan Formula is based on fine, pure dairy products, it has a fresh milk flavor. Patients can vary this flavor by simply adding 3 to 4 teaspoons of instant coffee, or 1½ teaspoons of any of their favorite extracts, like vanilla, per quart.

AN EFFECTIVE, FLEXIBLE PLAN

The Carnation Weight Reduction Plan provides balanced nutrition. Providing 1000 calories a day, the Plan gives the dieter 70 grams of high-quality, hunger-appeasing protein. This concentration of protein helps satisfy the appetite, and at the same time, keeps up the dieter's energy. The Plan meets the Daily Adult Requirement for all vitamins and minerals with established minimums.



The physician prescribes the multi-vitamin-mineral preparation to supply the vitamin-mineral elements outside the basic food drink. The physician may also wish to vary the number of meals the dieter replaces with the Carnation Plan Formula and the number of days the patient stays on the regimen. In this way the physician is given the opportunity to adjust the regimen of the dieter to suit the needs of *each* individual patient.

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Riboflavin (B_2)	8.6 Mg.	7
Niacinamide	16.8 Mg.	1.6
Iron	11.8 Mg.	1.1
Calcium	2.7 Gm.	3
Phosphorus	2.1 Gm.	2.8
Iodine	0.56 Mg.	5.6
Pyridoxine (B_6)	1.42 Mg.	**
Ca Pantothenate	11.8 Mg.	**
Vitamin B_{12}	2.0 Mcg.	**
Vitamin E	10.6 Units	**
Sodium	1.1 Gm.	**
Potassium	3.0 Gm.	**
Manganese	1.0 Mg.	**
Magnesium	1.3 Gm.	**
Copper	1.6 Mg.	**
Zinc	8.0 Mg.	**
Calories	1000	

**Calculations are based on a standard multi-vitamin-mineral supplement, 1½ cups Carnation Instant Nonfat Dry Milk, and 1 quart of whole milk.*

***M.D.R. (Minimum Daily Requirement) has not been established.*

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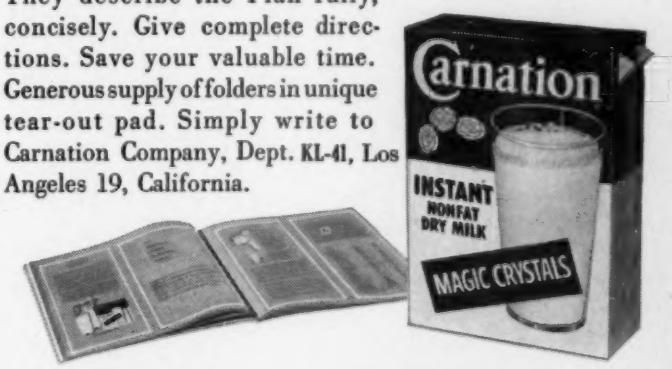

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The American Journal of Cardiology

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EDITORIAL

Classification of Pulmonary Hypertension

PULMONARY HYPERTENSION exists when the blood pressure within the pulmonary artery exceeds the uppermost normal limits (30/15 mm. Hg).[1] The term pulmonary hypertension is not well defined; as such it covers the whole pulmonary circuit. Hence, this definition of pulmonary hypertension is inaccurate because it gives no idea whatsoever about the pressure in the pulmonary capillaries or the pulmonary veins. For this reason, the pulmonary vascular tree must be divided into two sections both from an anatomical and functional point of view, the arterial and the venous or venocapillary[2,3] (Fig. 1). The arterial section begins with the pulmonary artery at the level of the pulmonary valves and ends with the small muscular arteries and arterioles; the venous or venocapillary section is comprised of the capillaries, the pulmonary veins and the left atrium up to the mitral valve. The left atrium should be included because of its hemodynamic importance.

Classically, the systemic arterial blood pressure is considered to be maintained by five factors; namely, the cardiac output, the blood volume, the blood viscosity, the elasticity of the main arteries and the peripheral resistance. When these factors are studied in the normal pulmonary circuit the blood pressure is essentially maintained by the right ventricular output, which determines the pulmonary arterial flow, and the vascular resistance (Fig. 2). The resistance is produced primarily at the level of the small muscular arteries and arterioles as well as at the mitral valve.

Pulmonary Arterial Flow: Normally, the pulmonary vascular tree is quite distensible, being able to accommodate a large volume of blood with very slight increase in blood pressure. It is only when the blood flow increases above three times its normal value, that is, when it exceeds 15 L. per minute, that the blood pressure rises beyond its normal limits.[4–6] The pulmonary vascular pressure is maintained by a delicate balance between flow and resistance; as a whole, the lung has a wide range of adaptability. In normal subjects the resistances are lessened when the blood flow increases, the pressure being constant.[2,4–6]

Under abnormal conditions the increase of the pulmonary blood pressure also depends on the two aforementioned factors; namely, the pulmonary arterial blood flow and the vascular resistance. Both of them are elevated under such conditions (Fig. 3). Under pathologic conditions the blood flow through the pulmonary artery increases in congenital malformations of the heart with left to right shunt,[1,7] postpneumonectomy states,[8] and in congenital absence of one of the main branches of the pulmonary artery.[9]

Pulmonary Vascular Resistance: When the pulmonary vascular tree is altered either through a reduction of its vascular bed or through a loss of pulmonary elasticity the level of the blood pressure will be elevated without an important increase in blood flow. This also happens in hypoxic conditions which lead to arteriolar constriction and consequently towards an elevation of the pulmonary arterial blood pressure.[6,10–12]

When pulmonary hypertension exists the resistance of the pulmonary vascular tree to blood flow may occur at different areas as follows: (1) in the pulmonary arteries (arterial area); (2) in the arteriolar and small muscular arteries (precapillary area); (3) in the interalveolar walls (capillary area); and (4) in the pulmonary veins, left atrium or mitral valve (postcapillary area) (Fig. 3). Generally speaking, functional changes should be considered very important in the genesis of pulmonary hypertension. I will briefly consider each one of those possibilities.

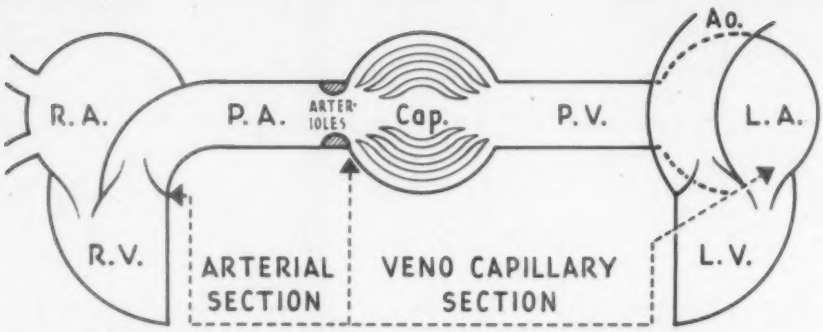

FIG. 1. Schematic representation of the pulmonary vascular tree and of the limits of the arterial and venocapillary sections. R. A. = right atrium; R. V. = right ventricle; P. A. = pulmonary artery, Cap. = capillaries; P. V. = pulmonary veins; L. A. = left atrium; L. V. = left ventricle; Ao. = aorta.

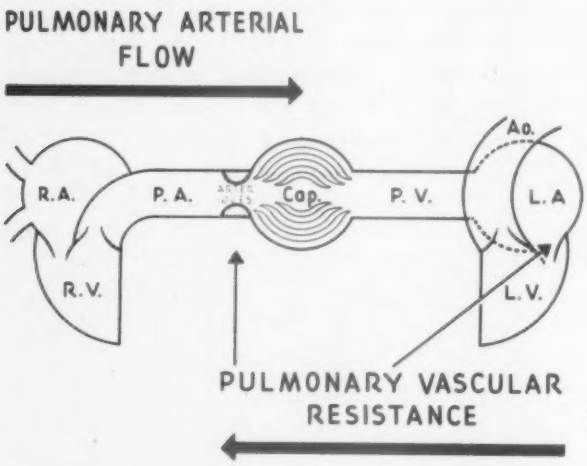

FIG. 2. Blood pressure of the pulmonary vascular tree under normal conditions, depending fundamentally on two factors: pulmonary arterial flow and pulmonary vascular resistance. Resistance is encountered mainly within the small muscular arteries and arterioles, and at the level of the mitral valve.

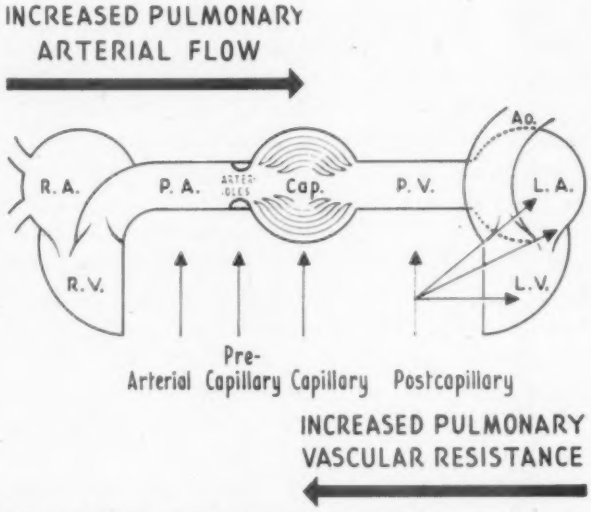

FIG. 3. Pulmonary hypertension depends on two factors: increased blood flow within the pulmonary artery and increased pulmonary vascular resistance. Subdivision of the pulmonary vascular tree into areas: arterial, precapillary, capillary and postcapillary.

The increased resistance within the *precapillary area* depends on the degree of functional narrowing of the arterioles and small muscular arteries and on the organic narrowing of these vessels. The abnormal functional narrowing or increased arteriolar vasoconstriction depends on several factors such as the increase of the capillary pressure as noted in mitral stenosis; curtailment of the capillary bed, an alteration noted in interstitial and parenchymatous diseases of the lung; decreased alveolar oxygen tension[10,11] as noted in alveolar hypoventilation syndromes and in hypoxemic states, as a result of alveolar hypoventilation and alveolarcapillary block.

The resistance to the blood flow in the *left atrium* under normal conditions depends on the following three main factors: (1) the mitral valve area, (2) the diastolic filling pressure of the left ventricle and (3) the amount of blood that flows through the atrium. In abnormal conditions the resistance to blood flow in the left atrium also depends on these three factors and in rare instances others may be revealed, such as tumor-like structures (thrombi, myxomas[13]) and septa[14] in the atrium. The resistance in the left atrium will be related to the reduction of the mitral valve area as in mitral stenosis, or to the height of the diastolic filling pressure in the left ventricle as in left heart failure. In any case the final result will be an elevation of the blood pressure in the venocapillary section and later in the arterial section as well.

The other places in the pulmonary vascular system where resistance to blood flow may be

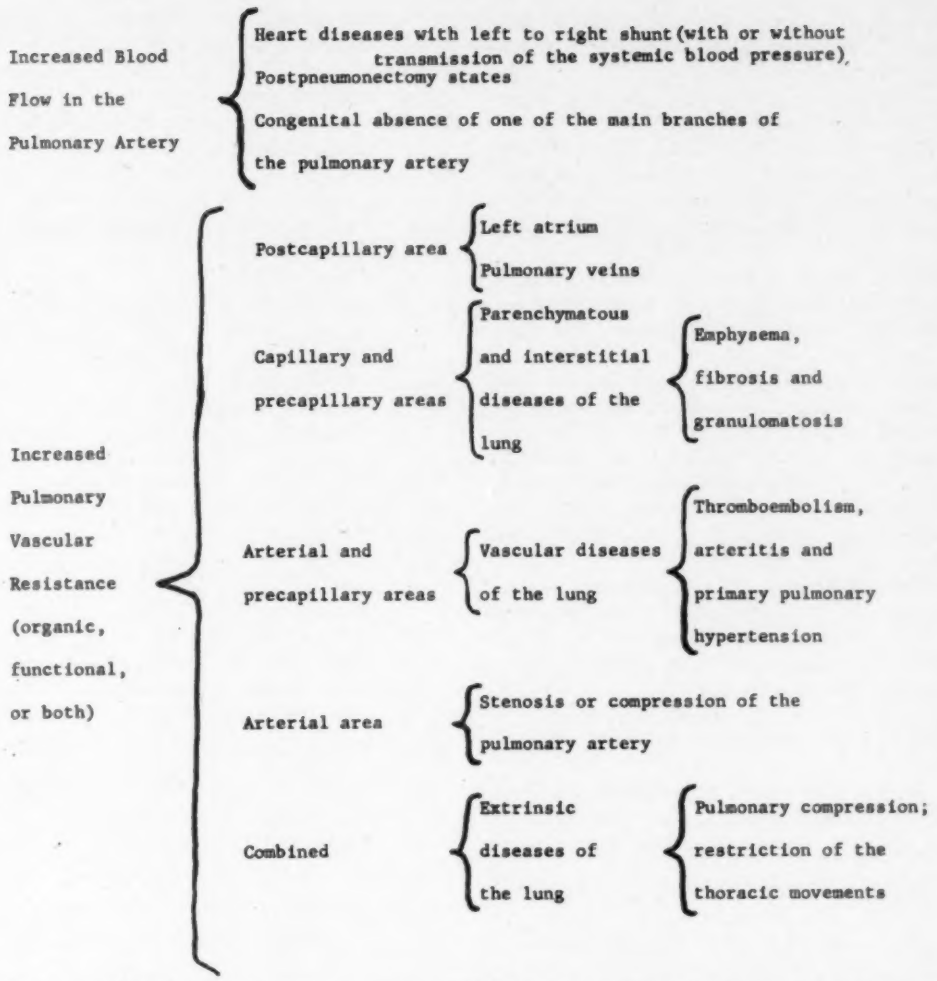
Increased Blood Flow in the Pulmonary Artery
Heart diseases with left to right shunt (with or without transmission of the systemic blood pressure)
Postpneumonectomy states
Congenital absence of one of the main branches of the pulmonary artery
Increased Pulmonary Vascular Resistance (organic, functional, or both)
Postcapillary area
Left atrium
Pulmonary veins
Capillary and precapillary areas
Parenchymatous and interstitial diseases of the lung
Emphysema, fibrosis and granulomatosis
Arterial and precapillary areas
Vascular diseases of the lung
Thromboembolism, arteritis and primary pulmonary hypertension
Arterial area
Stenosis or compression of the pulmonary artery
Combined
Extrinsic diseases of the lung
Pulmonary compression; restriction of the thoracic movements

FIG. 4. Classification of pulmonary hypertension. Increased blood flow is not always found at the origin of the pulmonary artery; it may begin within one of its main branches; for example, in patent ductus arteriosus, postpneumonectomy states, etc. Under the heading of extrinsic diseases of the lung are considered all functional or structural alterations of the lung produced by the following extrapulmonary diseases: deformities of the thoracic cage, thoracic myopathies and extreme obesity, major adhesive pleuritis and pleural effusions and bronchial or mediastinal tumor formations.

offered are the *pulmonary veins*, when their cross section is reduced, either congenitally[15–17] or by thrombus formation[18] or through external compression;[13] and the *interalveolar walls*, as occurs in interstitial or in parenchymatous diseases of the lung which reduce the capillary area; and in the *trunk of the pulmonary artery* or its main branches as in thromboembolism and stenosis[19,20] or compression of these vessels.

Proposed Classification of Pulmonary Hypertension: Now that the general outline has been briefly considered, touching on the fundamental physiologic and physiopathologic aspects, a classification is proposed based on this functional and anatomical reasoning (Fig. 4).

Any classification should not be so rigid as to impose a clear-cut differentiation between its different groups, since one form may merge into the other; its purpose is only to clarify and organize the fundamental biologic processes concerned. A certain case may initially fit into one of the groups but later may acquire characteristics that places it into several groups at the same time or may even place it in another group. Furthermore, some of the functional and structural alterations may well be reversible as a result of the removal of the offending cause.

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Clinical Studies

Anatomic and Electrocardiographic Correlation of Fallot's Tetralogy

A Study of 100 Proved Cases*

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Philadelphia, Pennsylvania

ELECTROCARDIOGRAPHIC PATTERNS associated with the tetralogy of Fallot have been described by Woods,[1] Donzelot et al.[2] and Sodi-Pallares et al.[3] The purpose of the present study was to correlate the electrocardiographic and hemodynamic alterations, to establish the incidence of so-called characteristic electrocardiographic findings, and to present electrocardiographic abnormalities which have not been heretofore stressed. One hundred proved cases of Fallot's tetralogy were analyzed.

METHODS

All cases were evaluated by right heart catheterization prior to surgery. In many cases angiocardiography was also performed. Right heart catheterization was carried out according to the routine of our laboratory. Sleep was induced in infants and children usually by sodium pentobarbital. One blood sample was secured from the axillary or jugular vein, one from each vena cava, three from the right atrium, two or three from the right ventricle and two from the pulmonary circuit and aorta if these vessels could be entered. Oxygen content determinations were made employing the Van Slyke apparatus. In all patients pressure recordings were made using an electromanometer and direct writing polyoscillograph (Sanborn) or a strain gauge manometer and photooscillograph (Electronics for Medicine). Both instruments were calibrated against a mercury manometer.

Twelve lead electrocardiograms were secured in all. When electrocardiographic evidence for right ventricular hypertrophy was not seen in lead V_1, leads further to the right (V_3R and V_4R) were recorded. All diagnoses were confirmed by surgical exploration or necropsy.

RESULTS

Age and Sex: The mean age was 7.3 years, with a range from three months to thirty-five years. There were sixty male and forty female patients in this group.

Cardiac Rhythm: Regular sinus rhythm was present in all but one patient. He had an atrial tachycardia. Nodal premature systoles were seen in two instances and ventricular premature beats in one case.

P-R Interval: The P-R interval was 0.143 ± 0.004† second. In five patients a first degree heart block was present and in one patient second degree heart block with Wenckebach periods. The P-R intervals ranged from 0.22 to 0.28 second in these patients.

P Waves: The P waves were considered normal in 50 per cent of the cases. In 28 per cent they were tall and peaked in limb lead II; in 11 per cent in both limb lead II and in one of the right precordial leads (V_1 or V_2); in 6 per cent in one of the precordial leads alone (usually V_2). In three cases the P waves were widened and notched only, and in one case they were deeply inverted in the right precordial leads.

The frontal plane distribution of $\hat{A}P$ was $-30°$ to $+70°$ with a mean of $+38°$. In the majority of cases it was found within the limits of $+20°$ to $+50°$ (Fig. 1).

QRS Duration and Axis: The QRS duration was normal in almost all instances (mean 0.067 ± 0.002 second). The frontal plane

† Standard error of the mean.

* From the Departments of Medicine and Pediatrics, Hahnemann Medical College, Philadelphia, Pennsylvania.

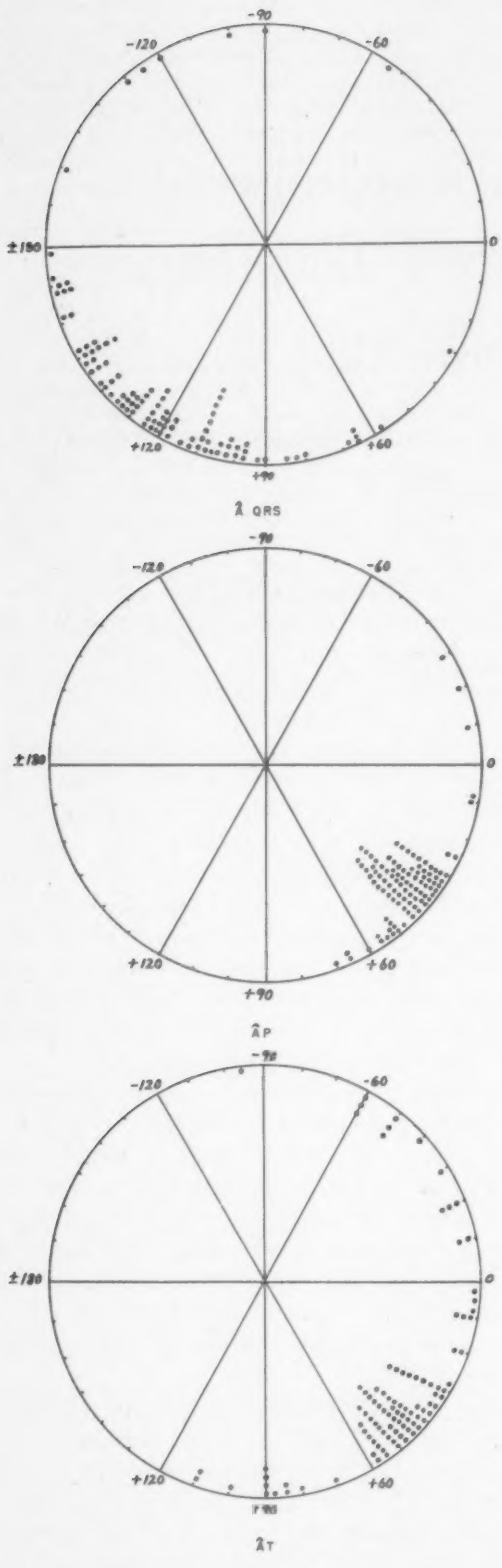

FIG. 1. Electrocardiographic axes. The ÂQRS was most frequently seen between +100° and +170°. ÂP and ÂT were of no diagnostic significance.

ÂQRS varied from −54° through +30° with the majority of cases within the +100° to +170° range. The mean ÂQRS was +135° (Fig. 1). A right axis deviation was present in 96 per cent of the cases.

QRS in V_1: In all but six cases the R/S ratio in V_1 was greater than 1 and was considered as evidence of right ventricular hypertrophy. The mean height of the R wave in V_1 was 17.32 ± 0.75 mm. and the R/S ratio 12.49 ± 0.99. In the forty-four cases in which the R/S ratio was greater than 1 in lead V_2, the mean height of R was 19.25 ± 1.17 mm.

An R or Rs was seen in sixty-nine cases with a definite notching or slurring on the upstroke of the R wave in forty-nine of these cases. A qR was seen in eight, a qRs in three, an rsR′ in nine, and an RS or rS in eleven of the cases (Fig. 2).

QRS in V_6: The most frequent configuration in this lead was rS (fifty-one cases). A qrS was seen in twenty and an RS in nine cases. In the other twenty of the patients the R/S ratio was greater than 1 in V_6 as well as in V_1. Of these, an Rs was seen in nine instances, a qRS in six, a qR in two and an R in three cases (Fig. 2). The mean height of R in those cases in which the R/S in V_6 was greater than 1 was 4.15 ± 0.79 mm.

QRS in aVR: The R/S ratio in aVR was greater than 1 in sixty-four of the patients. The mean amplitude of the R wave in these cases was 8.13 + 0.039 mm.

Transition Zone: In a majority of cases the transition zone in the precordial leads was shifted to the left of V_5 (sixty-seven cases).

ST-T Segments: In seventy-seven of the patients the T wave was upright in V_1 or V_2 through V_6. In eight of the cases T wave inversion persisted from the far right precordial leads to V_3; in three cases, to V_4 and in ten cases, to V_5 or V_6. S-T depression was never more than 1.5 mm.

Right Ventricular Pressure: The mean right ventricular pressure was 85.28 ± 2.21 mm. Hg. In a majority of cases the right ventricular pressure was between 70 and 90 mm. Hg, approaching but not exceeding the systemic pressure. As can be seen in Figure 3, there was no correlation between the right ventricular pressure and the height of R in V_1.

COMMENTS

The electrocardiographic patterns associated with tetralogy of Fallot fell essentially into

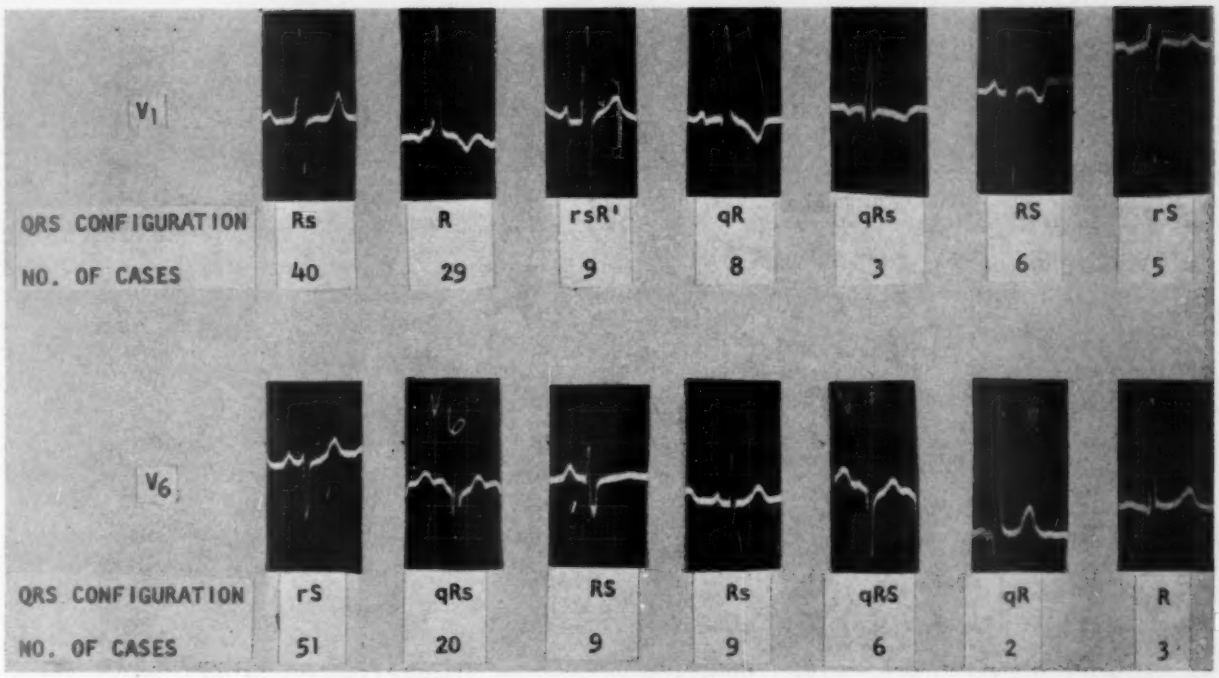

FIG. 2. The configuration and incidence of V_1 and V_6 complexes in 100 cases of tetralogy of Fallot. (Notching on upstroke of R wave, rsR's, are considered rsR′ equivalents.)

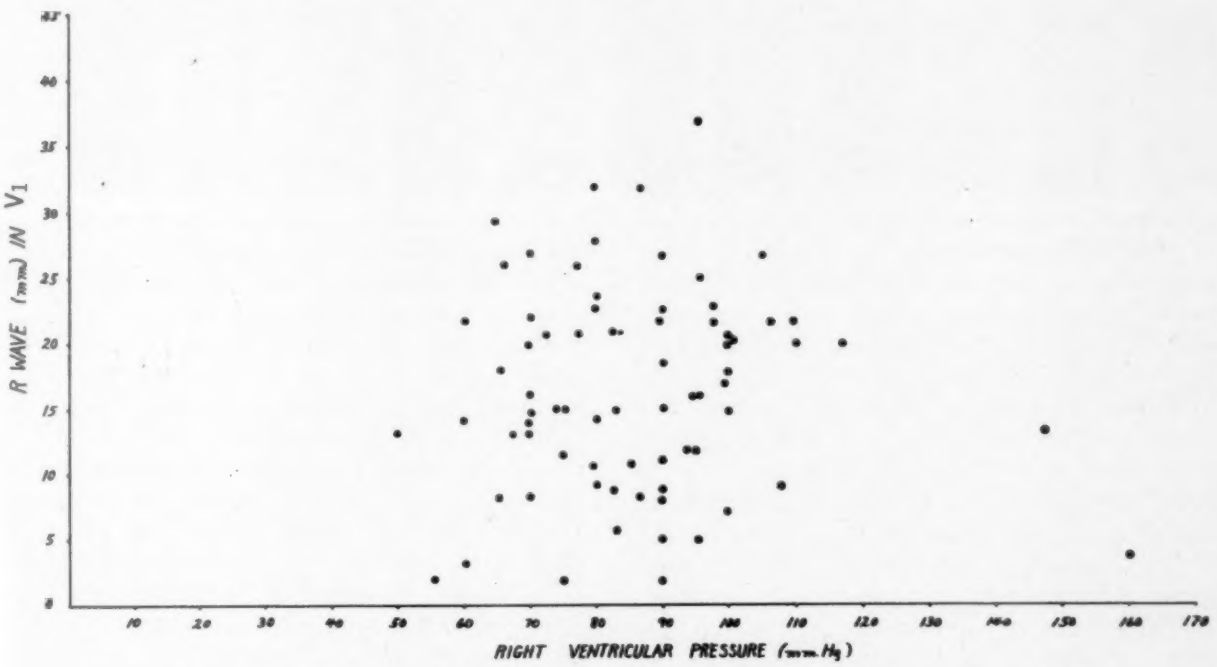

FIG. 3. The correlation of the right ventricular pressure with the height of the R wave in lead V_1.

three groups (Fig. 4). *Group A* (*forty-one cases*) was unmistakably diagnostic of severe right ventricular hypertrophy with a marked right axis deviation and clockwise rotation, ÂQRS 140° to 170°, a predominant R in aVR, a tall, slurred or notched R in V_3R and V_1 with deep S waves in V_2 through V_6. However, as can be seen in Figure 5, these electrocardiograms could not be distinguished from many cases of pure pulmonic stenosis. *Group B* (*forty-five cases*) resembled the first group in the standard and unipolar limb leads. Unlike this group, however, a predominant R wave was seen in V_1 through V_6. A qR or

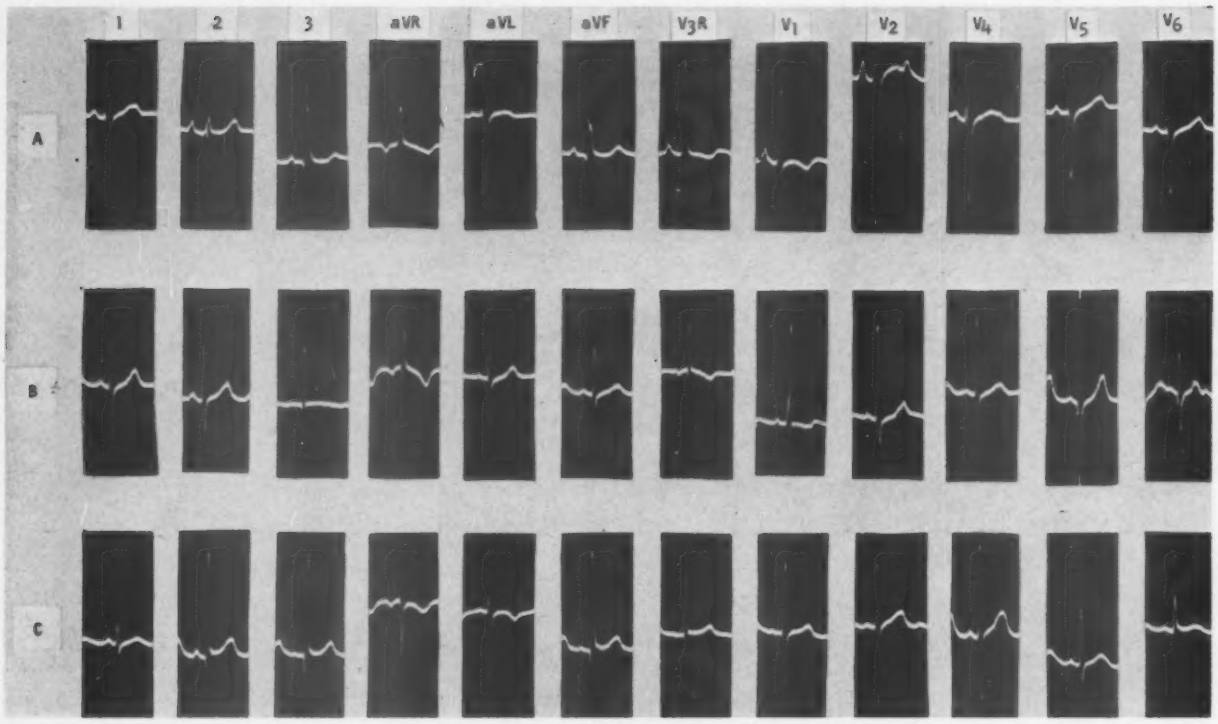

FIG. 4. The three preponderant electrocardiographic patterns associated with Fallot's tetralogy. Group A (forty-one cases): RVP 100/0; group B (forty-five cases): RVP 74/0; group C (fourteen cases): RVP 73/3 mm. Hg. Groups A and B were indistinguishable from pulmonic stenosis. Group B curves are commonly seen in ventricular septal defect. Group C curves are seen in many congenital cardiac lesions in which right ventricular hypertrophy is expected.

qRs configuration associated with an upright T wave was frequently seen in V_6. Group B electrocardiograms were frequently confused with those seen in ventricular septal defect and in pulmonic stenosis (Fig. 5). *Group C (fourteen cases)* represented an indeterminate electrocardiographic pattern which is seen in many cases of congenital heart disease associated with right ventricular hypertrophy. Frequently, the diagnosis of right ventricular hypertrophy was made only by the finding of a predominant R wave in V_3R or V_4R. A right heart strain pattern would not have been suspected from the rS or RS complexes in V_1 of these curves.

The important electrocardiographic combinations suggesting the presence of tetralogy of Fallot may be summarized as follows: (1) right ventricular hypertrophy (R/S in V_1 greater than 1), (2) a shift of the transition zone to V_5 or beyond, (3) a frontal plane ÂQRS between 100° and 170° and (4) inversion of the T waves in V_3R and V_1 but becoming upright from V_2 through V_6. Associated findings worthy of comment were tall and peaked P waves in lead II or V_2 and an R/S ratio greater than 1 in aVR.

Differentiation of Tetralogy of Fallot and Other Congenital Lesions: The unmistakable slurring or notching in the upstroke of the R wave in the right precordial leads is common in both pure pulmonic stenosis and tetralogy of Fallot. Furthermore, there is no apparent distinction of the vectorcardiogram in these two congenital cardiac lesions. Both demonstrate electrocardiographic evidence of marked right ventricular hypertrophy. It is obvious that the electrocardiographic differentiation of tetralogy of Fallot from pure pulmonic stenosis is impracticable. In fact, the electrocardiograms seen in pulmonic stenosis,[4] especially in groups II and III with right ventricular pressures from 60 to 110 mm. Hg, are indistinguishable from those of tetralogy of Fallot (Fig. 5). However, when the right ventricular pressure in pulmonic stenosis exceeds that of the left ventricle (group IV, 110 mm. Hg or greater) both right ventricular hypertrophy and marked ST-T depression indicative of ischemia usually appear in the electrocardiogram. This latter finding was seen in only six instances of tetralogy of Fallot. The electrocardiographic features in keeping with tetralogy of Fallot are commonly seen in cases of ventricular septal defect, patent ductus arteriosus with right to left shunts and

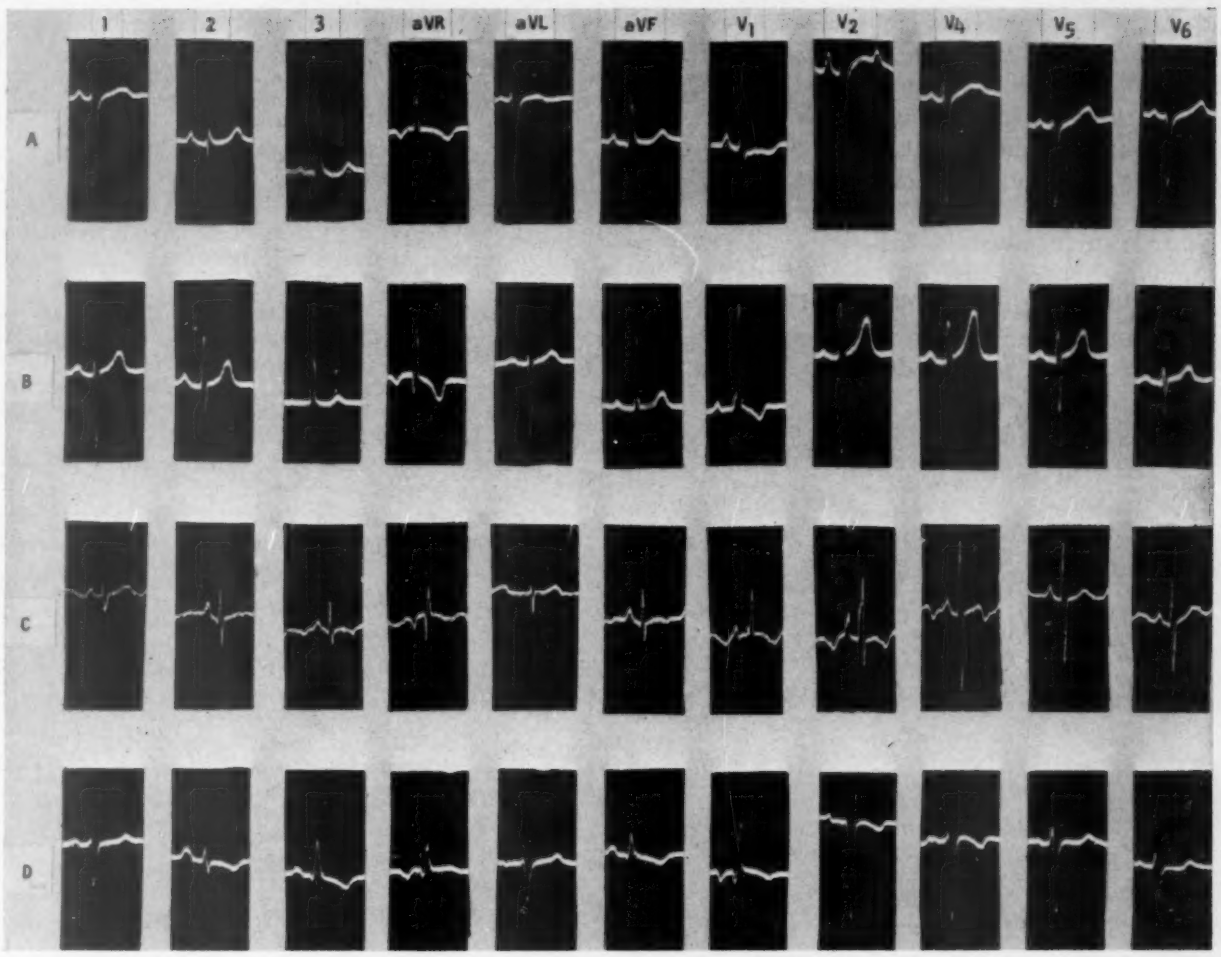

FIG. 5. Comparison of the electrocardiographic patterns of: (A) tetralogy of Fallot (RVP 100/0), (B) pure pulmonic stenosis (RVP 140/0), (C) ventricular septal defect (RVP 40/0) and (D) patent ductus arteriosus with right to left shunt (RVP 150/20). These lesions present similar electrocardiographic features.

in transposition of the great vessels (Fig. 5).

As expected from our previous studies of congenital heart lesions demonstrating right ventricular hypertrophy,[5] there was no apparent correlation between the height of R in V_1 and the right ventricular pressure (Fig. 3). Because of the anatomic arrangements in tetralogy of Fallot, the right ventricular pressure usually does not exceed that of the systemic ventricle and most of the right ventricular pressures lie in a narrow range (70 to 100 mm. Hg). This was true irrespective of the electrocardiographic configurations (Fig. 4) or patterns (Fig. 3). A normal electrocardiogram was seen in only four cases of tetralogy of Fallot. On the other hand, 30 per cent of ventricular septal defects[5] and 15 per cent of cases of pulmonic stenosis[4] were associated with normal electrocardiograms.

In conclusion, the electrocardiographic features described in this study are diagnostic of right ventricular hypertrophy. However, the patterns described will not distinguish pure pulmonic stenosis or right to left shunts associated with other congenital heart lesions from tetralogy of Fallot. The specific diagnosis, by the electrocardiographic method alone, of a congenital cardiac lesion demonstrating right ventricular hypertrophy should be made with reservation.

SUMMARY

1. The electrocardiographic features suggesting tetralogy of Fallot include: Right ventricular hypertrophy (R/S in V_1 greater than 1), a shift of the transition zone to V_5 or beyond, a frontal plane ÂQRS between 100° and 170°, and inversion of the T waves in V_3R to V_1, but becoming upright from V_2 through V_6.

2. Three groups of electrocardiographic patterns were noted: group A (forty-one cases) suggested severe right ventricular hypertrophy and clockwise rotation. Group B (forty-five

cases) was suggestive of right ventricular hypertrophy but less clockwise rotation was present. A tall R wave in V_1 associated with a qRs complex in V_6 was common. Groups A and B could not be differentiated from pure pulmonic stenosis and group B was suggestive of ventricular septal defect. Group C (fourteen cases) presented an indeterminate pattern. Right ventricular hypertrophy was diagnosed only by leads taken to the right of V_1. This group was frequently seen in many cases of ventricular septal defect, patent ductus and pulmonic stenosis.

3. There was no apparent correlation of right ventricular pressure and the height of R in V_1.

4. The anatomic diagnosis by the electrocardiographic method alone of a congenital heart lesion in which right ventricular hypertrophy is expected is hazardous.

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Right Ventricular Hypertrophy

Correlation of Electrocardiographic and Anatomic Findings*

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THE most widely used criteria for the electrocardiographic diagnosis of right ventricular hypertrophy in all probability are those devised by Sokolow and Lyon[1] in 1949 (Table I). More recently, some authors[2,3] have stated that the criteria of Sokolow and Lyon are too broad and, therefore, are likely to yield a significant number of erroneous diagnoses of right ventricular hypertrophy in the absence of heart disease.

The criterion of a delayed intrinsicoid deflection in lead V_1 or V_2 (ventricular activation time of 0.04 to 0.07 second) has little value in the electrocardiographic recognition of right ventricular hypertrophy according to our experience and that of Milnor.[3] Likewise, we are of the opinion that it is rather superfluous to consider the presence of an S wave in V_1 of less than 2 mm. in amplitude as being indicative of right ventricular hypertrophy, since this finding almost always is associated with an R/S amplitude ratio in V_1 greater than 1. (The converse does not necessarily hold true however.) In support of this belief is the report of Walker and associates[4] in which ten of twelve cases of right ventricular hypertrophy studied had an S wave in V_1 less than 2 mm. in depth and in every instance the R/S amplitude ratio in V_1 exceeded 1. If one considers yet another of the criteria of Sokolow and Lyon, namely, inversion of the T wave in lead aVL or aVF in the presence of an R wave greater than 6 mm. in amplitude, it is quite apparent that not only is this finding not specific for right ventricular hypertrophy alone (since there are other abnormalities such as left ventricular hypertrophy which can produce the same finding), but it is also observed not infrequently in the electrocardiograms of perfectly normal subjects. It is equally obvious that Sokolow and Lyon's criterion of an R wave of less than 5 mm. in amplitude in V_5 or V_6 is not satisfactory since such waves are frequently observed in the electrocardiograms of patients without right ventricular hypertrophy. The presence of an R wave in aVR 5 mm. or more in amplitude is probably of greater value in the diagnosis of right ventricular hypertrophy in children than it is in adults, while the ratio of R/S in V_5: R/S in V_1 of 0.4 or less is perhaps too cumbersome to be of practical use in clinical electrocardiography. All of the above considerations merely exemplify some of the shortcomings of the criteria devised by Sokolow and Lyon, though similar criticisms can be leveled at those presented by many other authors.

The objective of this study was to determine the usefulness and reliability of the criteria listed in Table II. In addition we have attempted to reduce the number of criteria in Table II to a few having the following advantages over those of Sokolow and Lyon: (1) They should be able to be applied quickly and with little difficulty to the clinical interpretation of the electrocardiogram. (2) They should decrease the frequency of erroneously positive diagnoses of right ventricular hypertrophy; and (3) they should not lead to significant lowering of the incidence of correct diagnoses.

MATERIALS AND METHODS

Of the 1,328 autopsied cases whose electrocardiograms were reviewed, the tracings of 118 were selected for further study, the basis for selection being that each electrocardiogram had to satisfy at least one of the criteria listed in Table II and to have a QRS interval of 0.10 second or less. Electrocardiograms which presented RR′, RSR′, or RSR′S′ deflections

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TABLE I

Criteria for the Diagnosis of Right Ventricular Hypertrophy*

I. Voltage of the R and S waves and various ratios:
   (1) The R wave in V_1 is 7.0 mm. or more.
   (2) The S wave in V_1 is less than 2.0 mm.
   (3) The S wave in V_5 or V_6 is 7.0 mm. or more.
   (4) The sum of the amplitudes of the R wave in V_1 and the S wave in V_5 or V_6 exceeds 10.5 mm. in individuals over five years of age.
   (5) The R wave in V_5 and V_6 is less than 5.0 mm.
   (6) The ratio of the R to the S wave in V_5 and V_6 is 1.0 or less.
   (8) The ratio of R/S in V_5: R/S in V_1 is 0.4 or less.
   (9) The ratio of the R wave to the S wave in V_1 exceeds 4.0 in individuals under the age of five years.
   (10) The ratio of the R wave to the S wave in V_1 exceeds 1.0 in individuals over the age of five years.
II. Delayed onset of the intrinsicoid deflection (delayed ventricular activation time), 0.04 to 0.07 second in V_1 and/or V_2 (normal = 0.015 to 0.035 second).
III. Depression of the RS-T segment and inversion of the T wave:
   (1) in V_1, less often in V_2 and V_3, when the R wave equals or exceeds 5.0 mm.
   (2) in aVL or aVF, when the R wave equals or exceeds 5.0 mm.
IV. Marked right axis deviation of ÂQRS greater than +110° is suggestive but not in itself diagnostic of right ventricular hypertrophy.

* From Sokolow and Lyon.[1]

in lead V_1 were also included in the special study series provided that the QRS duration did not exceed 0.10 second. The widest QRS duration in any of the six extremity leads was used in determining the QRS interval. The R/S amplitude ratio in leads V_1 and V_5 or V_6 was determined by dividing the amplitude of the tallest R wave in the lead in question by the depth of the deepest S wave. The R waves were measured from the top of the P-R segment, and the S waves from the bottom of the S-T segment (Fig. 1).

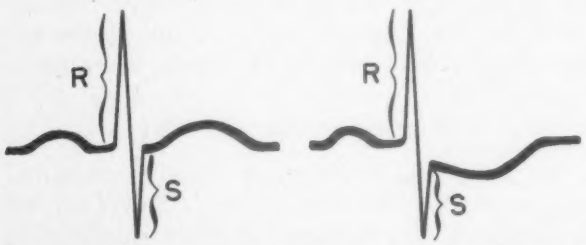

FIG. 1. Measurement of the amplitudes of the R and S waves. Left, the S-T segment is isoelectric; right, the S-T segment is depressed. In either case, the height of the R wave is measured from the upper portion of the baseline to the peak of the R, and the depth of the S wave is measured from the lower border of the baseline to the nadir of the S.

TABLE II

List of Criteria Studied

I. Voltage of the R and S waves and various ratios:
   (1) The R wave in V_1 is 7.0 mm. or more.
   (2) The S wave in V_5 or V_6 is 7.0 mm. or more.
   (3) The sum of the amplitudes of the R wave in V_1 and the S wave in V_5 or V_6 exceeds 10.5 mm. in individuals over five years of age.
   (4) The ratio of the R to the S wave in V_6 is 1.0 or less.
   (5) The R wave in aVR is 5.0 mm. or more.
   (6) R/S in V_5: R/S in V_1 is 0.4 or less.
   (7) The ratio of the R wave to the S wave in V_1 exceeds 1.0 in individuals over the age of five years.
   (8) The ratio of the R wave to the S wave in V_1 exceeds 1.0 and the R wave is 5.0 mm. or more.
II. Depression of the RS-T segment and inversion of the T wave in V_1 when the R wave equals or exceeds 5.0 mm.
III. Right axis deviation of ÂQRS (from +110° to −91°).

TABLE III

Anatomic Findings in 118 Cases

Findings	No. of Cases
Right ventricular hypertrophy	
Chronic pulmonary emphysema	12
Mitral stenosis	11
Chronic pulmonary emphysema and bronchiectasis	3
Pulmonic stenosis and interatrial septal defect	2
Chronic pulmonary emphysema and fibrosis	1
Bronchiectasis	1
Mitral stenosis, pulmonary emphysema and bronchiectasis	1
Cystic disease of the lungs	1
Primary pulmonary hypertension	1
Pulmonic stenosis	1
Interatrial septal defect	1
Total	35
Right and left ventricular hypertrophy	
Hypertensive cardiovascular disease	3
Rheumatic heart disease with chronic valvulitis	3
Chronic pulmonary disease (of varying type and causation)	6
Total	12
Left ventricular hypertrophy	33
Myocardial infarction	20
Heart grossly normal	15
Dextrocardia	1
Pulmonary embolism with right ventricular dilatation	2
Total	118

TABLE IV
Electrocardiographic Findings*

Anatomic Findings	RAD of ÂQRS	R in aVR = or >5.0 mm.	R in V_1 = or >7.0 mm.	R/S in V_1 >1	R/S in V_1 >1 R = or >5.0 mm.	S-T Depressed and T Inverted in V_1 with R = 5.0 mm.	R in V_1 + S in V_5 or V_6 >10.5 mm.	S in V_5 or V_6 = or >7.0 mm.	R/S in V_6 = or <1	R/S in V_5: R/S in V_1 = or <0.4
Right ventricular hypertrophy	25	5	9	17	9	11	17	16	18	12
Right and left ventricular hypertrophy	1	...	2	3	2	...	6	10	3	...
Left ventricular hypertrophy	1	1	2	3	...	...	21	29	4	1
Myocardial infarction	6	...	...	2	1	...	9	13	3	1
Normal	1	...	2	2	1	1	7	10	3	0
Dextrocardia	1	1	1	1	1	...	1	1	1	1
Pulmonary embolism with right ventricular dilatation	...	...	...	...	...	...	2	2	1	0
Total	35	7	16	28	13	12	63	81	33	15

* All figures in columns represent number of cases.

Hereafter, this report will concern solely the 118 cases referred to previously. Patients in this group ranged in age between sixteen and eighty-four years.

In correlating the postmortem and electrocardiographic findings, anatomic right ventricular hypertrophy was considered present when the right ventricular wall measured 5 mm. or more in thickness and the heart weight was greater than the expected normal.[4] In one case included in the group with anatomic right ventricular hypertrophy, the right ventricular wall was only 4 mm. thick but there was coexisting right ventricular dilatation.[4] Anatomic left ventricular hypertrophy was present when the left ventricular wall was 13 mm. or more in thickness;[5] combined ventricular hypertrophy was considered to be present when the above anatomic criteria for both right and left ventricular hypertrophy were satisfied.

RESULTS

In Table III the anatomic findings at postmortem study are presented in the 118 cases whose electrocardiograms satisfied one or more of the criteria cited above for the diagnosis of right ventricular hypertrophy. These findings in turn are related in Table IV to each of the electrocardiographic criteria cited in Table II, the values signifying the number of cases with a given anatomic diagnosis whose electrocardiograms satisfied the criterion in question. As indicated in Table III, of the 118 electrocardiograms satisfying at least one of the criteria for the electrocardiographic diagnosis of right ventricular enlargement only forty-seven cases were found at postmortem to have anatomic right ventricular hypertrophy (with or without coexisting left ventricular hypertrophy), so that there was a 60 per cent incidence of erroneous electrocardiographic diagnoses of right ventricular hypertrophy in this group of cases (Table V).

The astonishing frequency of false positive electrocardiographic diagnoses of right ventricular hypertrophy was due in no small part to the relative lack of specificity of such criteria as the R in V_1 + S in V_5 > 10.5 mm. and the S in V_5 or V_6 = or > 7 mm. Thus, of the electrocardiograms satisfying one or the other of the aforementioned criteria for the diagnosis of right ventricular hypertrophy, approximately 60 per cent in each group represented false positive diagnoses. It is not surprising that twenty-one of sixty-three electrocardiograms meeting the criterion of an R in V_1 + S in V_5 or V_6 > 10.5 mm. had autopsy-proved left ventricular hypertrophy, since it is not uncom-

TABLE V

Comparison of the Diagnostic Efficacies of the Various Electrocardiographic Criteria for the Diagnosis of Right Ventricular Hypertrophy

Anatomic Findings	A*	B*	C*	D*	E*	F*
Right ventricular hypertrophy	35	34	34	30	26	31
Right and left ventricular hypertrophy	12	8	7	4	2	5
Left ventricular hypertrophy	33	8	6	4	1	4
Myocardial infarction	20	12	12	9	8	11
Normal	15	7	5	2	2	5
Dextrocardia	1	1	1	1	1	1
Pulmonary embolus	2	1	1	0	0	1
Total	118	71	66	50	40	58
Per cent of cases of right ventricular hypertrophy correctly diagnosed‡	100 (47)†	89.3 (42)	87.2 (41)	72.3 (34)	59.5 (28)	76.6 (36)
Per cent of cases of false positive diagnoses of right ventricular hypertrophy§	60	41	38	32	30	38

* *A*, criteria as listed in Table II (derived from Sokolow and Lyon[1]); *B*, RAD, R in $V_1 \geqq 7.0$ mm., R/S in $V_1 > 1$, R/S in $V_6 \leqq 1$; *C*, RAD, R/S in $V_1 > 1$, and/or R/S in $V_6 \leqq 1$; *D*, RAD and/or R/S in $V_1 > 1$ regardless of the R wave amplitude; *E*, RAD and/or R/S in $V_1 > 1$ with the R being 5.0 mm. or more (Milnor[3]); *F*, RAD and/or R/S in $V_1 > 1$ with the R being 5 mm. or more and/or R/S in $V_6 \leqq 1$.

† The figures enclosed in parentheses represent the numbers of cases satisfying the criteria.

‡ The percentage of cases of right ventricular hypertrophy correctly diagnosed was obtained by dividing the total number of cases diagnosed as right ventricular hypertrophy into the number of cases in this group having anatomic right ventricular hypertrophy or right and left ventricular hypertrophy.

§ The percentage of cases of false positive diagnoses of right ventricular hypertrophy was determined by dividing the total number of cases diagnosed as right ventricular hypertrophy into the number of cases in this group with anatomic findings other than right ventricular or combined ventricular hypertrophy.

mon to find in electrocardiograms of patients with left ventricular enlargement a relatively deep S wave in V_5 or V_6 due to posterior rotation of sÂQRS. This is likewise true in the case of the criterion of an S in V_5 or V_6 = or > 7 mm. For these reasons we recommend that the criteria of an R in V_1 + S in V_5 or $V_6 > 10.5$ mm. and S in V_5 or V_6 = or > 7 mm. be abandoned.

In the electrocardiograms of seven of the thirty-five cases with anatomic right ventricular hypertrophy, R in aVR was 5 mm. or more in amplitude. In six of the seven tracings there was coexisting right axis deviation of ÂQRS (to the right of +110°) while in the remaining electrocardiogram the R/S amplitude ratio in V_1 was greater than 1. Of the twelve cases with anatomic right ventricular hypertrophy whose electrocardiograms met the criterion of a depressed S-T segment and inverted T wave in V_1 with an R wave of 5 mm. or more amplitude in that lead, all twelve cases presented the additional electrocardiographic finding of an R/S amplitude ratio in V_1 exceeding 1. Fifteen electrocardiograms satisfied the diagnostic criterion of an R/S in V_5: R/S in V_1 = or < 0.4; but in twelve of these electrocardiograms there was also an R/S amplitude ratio in lead $V_1 > 1$, and in the remaining three cases right axis deviation of ÂQRS was present.

There would seem to be one conclusion to be drawn from these observations. The criteria of an R in aVR ≧ 5 mm., a depressed S-T segment and inverted T wave with an R wave of 5 mm. or more in lead V_1, and an R/S in V_5: R/S in V_1 = or < 0.4 can be considered superfluous insofar as their practical value in the electrocardiographic diagnosis of right ventricular hypertrophy is concerned; because if any of these criteria are fulfilled, one or a combination of the following findings will also be present: (1) right axis deviation of ÂQRS (to the right of +110°); (2) R/S amplitude ratio in V_1 greater than 1; (3) R/S amplitude ratio in V_6 equal to or less than 1.

An R wave in lead V_1 of 7 mm. or more was observed in sixteen electrocardiograms and was accompanied in eleven of these records by an R/S amplitude ratio in $V_1 > 1$. In the remaining five cases an R wave in V_1 equal to or greater than 7 mm. was the sole abnormality; two of the cases had normal hearts at postmortem study; two showed left ventricular hypertrophy; and the remaining case had anatomic

evidence of combined ventricular hypertrophy.

Right axis deviation of ÂQRS (to the right of +110°) was observed in the electrocardiograms of thirty-five cases, twenty-six of which were found to have anatomic right ventricular hypertrophy at postmortem. In six of the remaining nine cases, myocardial infarction was responsible for the right axis deviation of ÂQRS observed in the electrocardiograms. There is rarely any difficulty in differentiating right axis deviation due to infarction from that due to right ventricular hypertrophy since in the former other abnormalities related to the infarction will be present. Thus, lead I in right axis deviation due to myocardial infarction tends to show the Qr type of QRS configuration, while in right axis deviation associated with right ventricular hypertrophy the QRS configuration in this lead is of the rS type. Right axis deviation of ÂQRS was the sole abnormality in twelve cases, seven of which had myocardial infarction on postmortem study; four cases had right ventricular hypertrophy; and in the remaining one, a grossly normal heart was found.

An R/S amplitude ratio in V_1 exceeding 1 (regardless of the actual R wave amplitude) was observed in twenty-eight of the electrocardiograms in the group of 118 cases studied. Twenty of the twenty-eight cases were found to have anatomic right ventricular hypertrophy at postmortem. This electrocardiographic finding was the sole abnormality in the electrocardiograms of twelve cases, five of which had anatomic right ventricular hypertrophy alone; one showed evidence of right and left ventricular hypertrophy; two satisfied the criteria of left ventricular hypertrophy; two had myocardial infarction; and the remaining two had grossly normal hearts.

The combined criteria of an R/S amplitude ratio in $V_1 > 1$ and an R wave in this lead of 5 mm. or more were noted in thirteen electrocardiograms, and ten of these patients showed anatomic evidence of right ventricular hypertrophy. The above two criteria were found as sole abnormalities in electrocardiograms recorded from four patients, one with anatomic right ventricular hypertrophy, one with combined ventricular hypertrophy, another with myocardial infarction and one with a grossly normal heart.

An R/S amplitude ratio in lead V_6 equal to or less than 1 was observed in the electrocardiograms of thirty-three patients, twenty-one of whom were demonstrated to have anatomic right ventricular hypertrophy at postmortem study. Of the fifteen patients presenting this finding as their only electrocardiographic abnormality, there were four cases with autopsy-proved right ventricular hypertrophy; three with right and left ventricular hypertrophy; two with left ventricular hypertrophy; two with myocardial infarction; two with grossly normal hearts; and finally one patient with pulmonary embolism.

In the study series of cases, we applied the following three criteria to the electrocardiographic diagnosis of right ventricular hypertrophy: right axis deviation of ÂQRS; R/S in $V_1 > 1$; R/S in $V_6 =$ or < 1. For the diagnosis of right ventricular hypertrophy to be made in a given electrocardiogram, the tracing had to present at least one of the three features cited above. However, the diagnostic accuracy of the electrocardiogram increased when two of the three criteria for right ventricular hypertrophy were satisfied; it was found that twenty-seven electrocardiograms met this requirement. Of this group twenty-three cases had autopsy-proved right ventricular hypertrophy. One case had combined ventricular hypertrophy; two showed left ventricular hypertrophy and one had dextrocardia.

Comparison of Various Criteria: Table V represents an attempt to define the relative diagnostic accuracies of single or varying combinations of electrocardiographic criteria for the diagnosis of right ventricular enlargement, including those of Sokolow and Lyon[1] listed in Table II, those recommended by Milnor[3] and those proposed by us. It can be seen that Milnor's criteria exhibited a relatively high percentage of correct diagnoses (that is relatively few false positive diagnoses) but missed right ventricular hypertrophy in a significant number of the cases. On the other hand, the criteria of Sokolow and Lyon, which are generally representative of the combination of criteria occupying the left side of Table II, yielded an impressively large number of false positive diagnoses of right ventricular hypertrophy. We consider our criteria to represent a medium between the two extremes just described in that they established the correct diagnosis in forty-one of the forty-seven cases of anatomic right ventricular hypertrophy and at the same time yielded far fewer erroneous diagnoses of right ventricular hypertrophy than did the criteria of Sokolow and Lyon.

Comments

Ideally in clinical electrocardiography, the criteria for the electrocardiographic diagnosis of a given abnormality such as right ventricular hypertrophy should possess the following attributes: (1) they should be few in number; (2) they should be easily applied to the routine electrocardiogram with a minimum of time and effort required; (3) they should yield an optimally high frequency of correct diagnoses of right ventricular hypertrophy with a correspondingly low incidence of false positive diagnoses; and (4) they should be equally applicable to right ventricular hypertrophy whatever its causation, whether due to congenital heart disease, chronic cor pulmonale or mitral stenosis.

The criteria proposed by some authorities, notably those of Sokolow and Lyon, would seem to be diagnostic in all or virtually all cases of right ventricular hypertrophy with electrocardiographic abnormalities but this quality is more than offset by the high incidence of false positive diagnoses yielded by these criteria and by their multiplicity and cumbersomeness. Furthermore, many of the criteria are useful primarily in the diagnosis of right ventricular hypertrophy due to congenital heart disease and fail completely in this purpose in electrocardiograms of patients with right ventricular hypertrophy due to chronic cor pulmonale or mitral stenosis. The criteria of Braunwald and associates,[2] though possessing much diagnostic merit, nevertheless are too involved to be useful in our opinion. However, Braunwald et al. can claim at least one advantage for their criteria and that is their applicability to the electrocardiograms of children as well as of adults. Despite this we are not convinced of the practical clinical usefulness of their criteria for the electrocardiographic diagnosis of right ventricular hypertrophy by the average cardiologists.

It is our belief that a closer approach to the ideal electrocardiographic criteria for the diagnosis of right ventricular enlargement are those proposed by Milnor[3] which consist of right axis deviation of ÂQRS ($+110°$ to $-91°$) or an R/S in $V_1 > 1$, the R in V_1 being greater than 5 mm. When Milnor's criteria were applied to the 118 electrocardiograms selected for special study, it was found that these criteria yielded the lowest incidence (30 per cent) of false positive diagnoses of right ventricular hypertrophy of any studied. On the other hand, the criteria of Milnor diagnosed only 59.5 per cent of the cases of right ventricular hypertrophy which is to be compared, for example, with the incidence of 72.3 per cent when the criteria of right axis deviation plus R/S in $V_1 > 1$ regardless of its amplitude were utilized and with 87.2 per cent when the criteria of right axis deviation, an R/S in $V_1 > 1$ and/or an R/S in $V_6 =$ or < 1 were utilized.

The criteria just cited were equally applicable on the whole to electrocardiograms of patients with right ventricular hypertrophy due to mitral stenosis or to chronic cor pulmonale as well as those with congenital heart disease. The same cannot be said for many of the diagnostic criteria proposed by other authors. Of pertinence in this regard is the fact that fourteen of our forty-seven cases with anatomically demonstrated right ventricular hypertrophy or combined right and left ventricular hypertrophy were clinically diagnosed as mitral stenosis; twenty-four cases were considered to have chronic cor pulmonale; four cases had congenital heart disease and in five cases with combined ventricular hypertrophy the cause of the cardiac abnormality was not entirely certain. The predominance of cases of mitral stenosis and chronic cor pulmonale in this study series as compared to the number of cases of congenital heart disease reflects merely the fact that the electrocardiograms passing through the Heart Station at Barnes Hospital are recorded almost exclusively from adults.

Conclusion

From the observations reported in this paper it is concluded that the following criteria are superior to those proposed by other authors to date in making the electrocardiographic diagnosis of right ventricular hypertrophy: (1) right axis deviation of ÂQRS (to the right of $+110°$); (2) an R/S amplitude ratio in $V_1 > 1$, and (3) an R/S amplitude ratio in $V_6 =$ or < 1. While only one of these criteria need be satisfied to suspect the presence of right ventricular hypertrophy, the diagnosis becomes more certain if two or more of these findings are present.

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The Normal QRS Vectorcardiogram in Infants and Children from Birth to Fifteen Years*

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PREVIOUS studies on the normal vectorcardiograms of infants and children have been limited to specific age groups. Lasser and Grishman[1] studied eight children whose ages ranged from eight months to eight years. Lamb and Dimond,[2] using their own system of electrode placement, studied forty-six patients with an age range of one day to ten years. Elek et al.[3] used about the same number of patients but limited the study to less than two years of age.

Schaffer and Beinfield[4] reported the normal vectorcardiogram of newborns up to seven days. They showed that the spatial vector loop of a normal newborn is identical with that of an adult with right ventricular preponderance. Castellanos et al.[5] were convinced that pathologic right ventricular hypertrophy in the newborn cannot be distinguished from "physiologic" right ventricular hypertrophy. They chose the age range from seven months to twelve years for their study in fifty-four patients. According to these authors, right ventricular hypertrophy in this age group is pathologic when the rotation of the loop is clockwise in the horizontal plane using Frank's system of electrode placement.[6] Recently, Rosen and Gardberg,[7] using both cube and tetrahedron systems for comparison, studied infants from birth to two and a half years. They found considerable variation in the progression of the normal vector loop in the horizontal plane of the cube and in the frontal plane of the tetrahedron system. A period of "transition" from the so-called "physiologic" right ventricular preponderance of the newborn infant to the adult pattern was first described by Elek et al.[3] They placed the "transition" anywhere from twenty-six to forty days or over.

The purpose of this communication is to report the normal spatial QRS vectorcardiogram of infants and children from birth to fifteen years, inclusive.

MATERIAL AND METHOD

A modification of the apparatus described by Shillingford and Brigden[8] was constructed by Hosterman and Wheeler.[9] This apparatus (Fig. 1) was used throughout the study and the methodology is as follows:

"Two simultaneous electrocardiograms are taken at 50 mm. per second on a Sanborn direct writing electrocardiograph using the vector lead system of Grishman.[10] The tracing obtained is placed on a table of the device where the pen track of one of the leads is followed at 0.01 second intervals by a lever which through a system of mirrors causes a point of light to travel in a horizontal axis on a sheet of paper. Simultaneously the other lead is followed by another lever which imparts the vertical motion to the same point of light. At each 0.01 second interval a pencil dot is made on the paper at the position of the light spot. The direction, magnitude and speed of the vector loop can thereby be traced, one of the leads representing a horizontal electrical axis and the other a vertical axis. By taking three pairs of leads the horizontal, frontal and sagittal vectors may be drawn—but of course not from the identical heart beat."[9]

Over 1,000 vectorcardiograms were taken by this method from 1951 to 1957 on patients admitted to Children's Hospital and normal infants and children brought to the heart laboratory exclusively for vectorcardiographic tracing. On the basis of clinical and radiologic data, 154 patients were found with normal hearts. The 166 QRS vectorcardiograms of these patients formed the material for this study. Their

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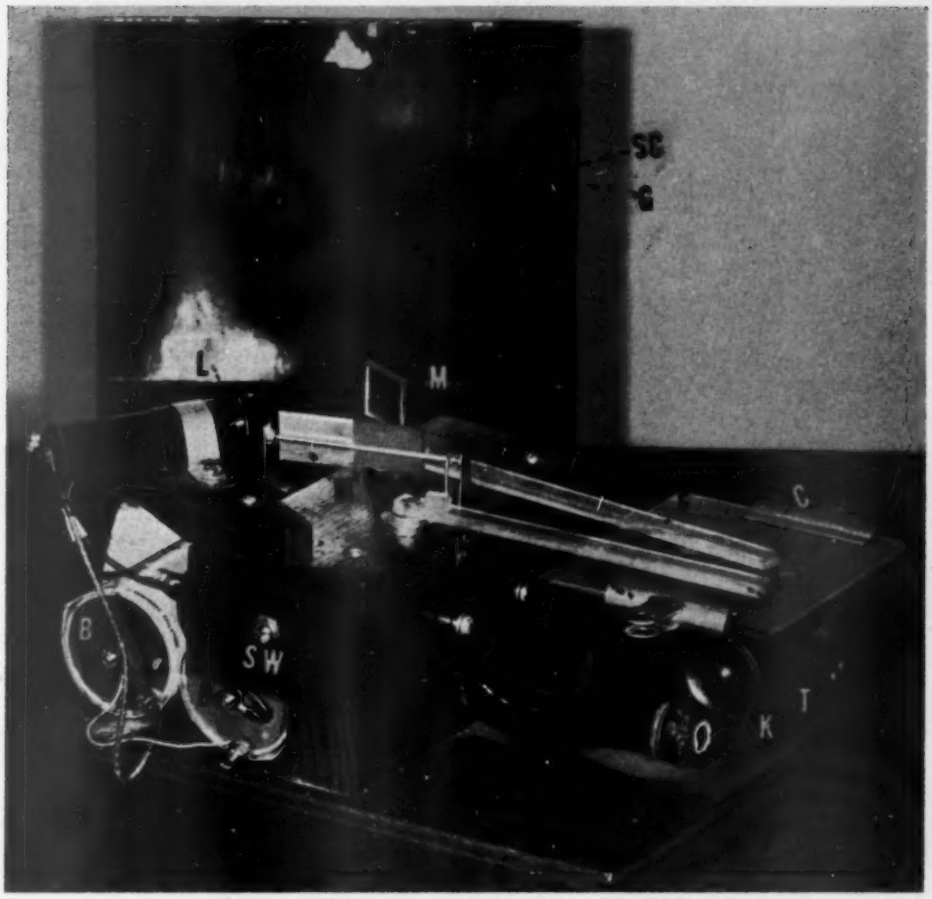

FIG. 1. Apparatus for recording vectorcardiograms. (M, M′) mirrors connected to plastic fingers (F, F′). Movement of (F) changes the position of (M) and moves the point of light from (L) in a horizontal direction on the screen (SC). Movement of the other finger (F′) changes the position of (M′) imparting a vertical motion to the point of light reflected from (M). (C) clips hold the electrocardiogram firmly on the table (T). (K) knob when turned moves the table to desired position for the fingers (F, F′). B = batteries; SW = switch; G = graph paper placed on the screen (SC).

ages ranged from birth to fifteen years, inclusive. The sex distribution was equal.

Only the QRS loops were examined for this study. The loops were analyzed in all the three planes for the following: (1) morphology of the loop; (2) rotation of the loop; (3) position of the 0.02, 0.03, 0.04 and 0.05 second instantaneous vectors.

The morphology of the loop was described in simple terms as triangular, elliptical and a figure of eight. Loops assuming other geometric patterns were classified as "indefinite." "Early transition" pattern in which the first part of the centrifugal limb begins to rotate counterclockwise, were also included in the "indefinite" group. The loops were also observed for open or closed configuration. The rotation of the loop was described as clockwise, counterclockwise or a combination of both. The 0.02, 0.03, 0.04 and 0.05 second vectors were plotted in all planes.

Six patients in this study were followed with serial vectorcardiograms for various lengths of time. The youngest was eight days and the oldest seven months.

Table I shows the age group distribution and Table II is a summary of the morphology and rotation of the loops in the different age groups.

TABLE I
Classification of Age Groups

Groups	Age	No. of Vectorcardiograms	
I	0–7 days	14	
	8–14 days	13	
	15 days–1 mo.	8	35
II	5–12 wk.	22	
	13 wk.–6 mo.	20	
	7–12 mo.	16	58
III	13 mo.–3 yr.	13	
	3–6 yr.	19	
	6–10 yr.	20	
	10–15 yr.	21	73
		Total	166

TABLE II
Summary of Morphology and Rotation of QRS Loops

Groups	Horizontal			Frontal			Sagittal		
	I	II	III	I	II	III	I	II	III
Triangular	4	5	7	4	4	3	1	4	7
Elliptical	9	8	30	3	7	24	9	5	17
Figure of eight	10	22	10	11	30	28	13	18	13
Indefinite	12	23	26	17	17	18	11	31	36
Open loop	2	7	0	2	5	0	4	7	0
Closed loop	33	51	73	33	53	73	31	51	73
CW*	15	3	0	19	20	7	17	37	58
CCW†	5	29	63	5	9	38	0	1	2
CW-CCW‡	4	0	0	1	17	17	18	17	13
CCW-CW§	11	26	10	10	12	11	0	3	0

* CW = clockwise rotation.
† CCW = counterclockwise rotation.
‡ CW-CCW = clockwise-counterclockwise rotation.
§ CCW-CW = counterclockwise-clockwise rotation.

RESULTS

GROUP I: (BIRTH TO ONE MONTH)

1. Birth to Seven Days: There were fourteen patients in this group. Seven patients were under four days of age. In the horizontal plane there were three figures of eight; two had as much left part of the loop as right, and only two were entirely in the right anterior quadrant. Two of the figures of eight had centrifugal limbs more anterior than the centripetal limbs and in the other one the reverse was true.

The 0.02 second instantaneous vector was directed exclusively anteriorly and predominantly to the right and inferiorly. Occasionally, it was oriented to the left and superiorly. The 0.03 second vector was oriented anteriorly equally to the right or to the left and inferiorly. The 0.04 second vector was widely scattered anteriorly or posteriorly to the right and inferiorly; whereas the 0.05 second vector was usually located posteriorly to the right near or at the E point.

From four to seven days a rapid shifting of the 0.03 second vector almost exclusively to the left, anteriorly and inferiorly took place; while the 0.02 second vector remained about the same or moved slightly to the left. More figures of eight were taking shape in the horizontal plane.

2. Eight to Fourteen Days: "Transition" forms either as complete forms of figures of eight or "early transition" patterns with the first part of the centrifugal limb starting to rotate counterclockwise dominated the morphology of the loop in the horizontal plane. For lack of a better term, the latter arrange ment is classified as "indefinite." However, a good number were triangular or eliptical with no suggestion of transformation into a figure of eight pattern.

3. Fifteen Days to One Month: Of the eight patients in this group only two had a definite figure of eight pattern in the horizontal plane. Two of the six patients who were followed with serial vectorcardiograms actually terminated their "transition" period in this age group. One of these had a figure of eight pattern at age eighteen days and a repeat vectorcardiogram at age thirty days showed a complete counterclockwise rotation although the mean QRS vector was located at +45 degrees in the horizontal plane. In the other patient, the figure of eight was present at age ten days and at age twenty-one days "transition" was complete with the mean QRS vector at +90 degrees and a counterclockwise rotation of the loop in the horizontal plane.

All patients of group I had clockwise rotation or clockwise-counterclockwise rotation in the sagittal plane, whereas in the frontal and horizontal planes there were as many clockwise as counterclockwise rotations. The 0.04 second vector was oriented either anteriorly or posteriorly to the right and the 0.05 second vector was directed posteriorly to the right close to the E point.

Comment: Rapid changes in the morphology

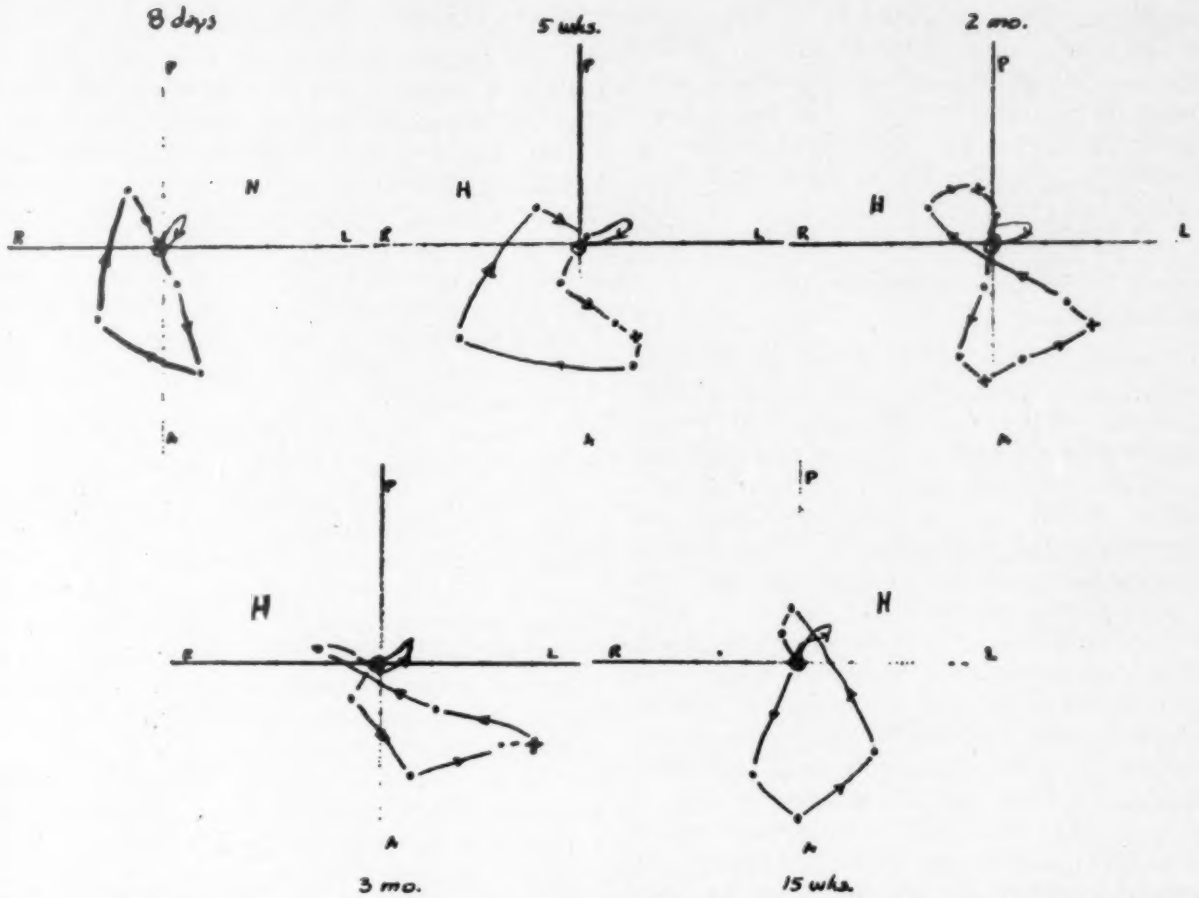

FIG. 2. Serial vectorcardiograms of patient, B. G., from eight days to fifteen weeks. Horizontal plane of the cube system of Grishman.

and rotation of the loop characterize the first month of life of a newborn. "Transition" forms can start even in the first three days of life and complete counterclockwise rotation can be seen as early as the third and fourth weeks in the horizontal plane. The most important vectors showing these changes in this group are the 0.02 and 0.03 second vectors. At birth they are situated anteriorly either to the right or left, inferiorly and, occasionally, superiorly. By the third and fourth weeks they are mostly oriented to the left, anteriorly and inferiorly. A few open loops are seen in all the three planes, but by far, most of the loops are closed.

GROUP II: (FIVE WEEKS TO ONE YEAR)

Five to Twelve Weeks: In the horizontal plane, figure of eight patterns were frequent. The latest onset of "transition" seen in this subgroup was at two months. There was one clockwise rotation with no tendency to an early formation of a figure of eight at age three months. The loop, however, was predominantly in the left anterior quadrant in the horizontal plane.

Thirteen Weeks to Six Months: Again, figure of eight patterns were common. There was no clockwise rotation in the horizontal plane. Because of the dominance of figure of eight patterns as in the previous subgroup (five to twelve weeks) rotation of the loop was frequently counterclockwise-clockwise.

Seven Months to One Year: Rotation in this subgroup was all counterclockwise in the horizontal plane. There were only occasional figures of eight.

Comment: "Transition" forms dominate the first two subgroups. The third subgroup (seven months to one year) has all counterclockwise rotation with only occasional figures of eight. The 0.02 and 0.03 second instantaneous vectors are directly to the left, anteriorly and inferiorly. The 0.04 second vector can point either to the right or left, anteriorly or posteriorly and inferiorly or, occasionally,

superiorly. This variability in the orientation of the 0.04 second vector is due to the fact that the centripetal limb may pass the E point either to the right or left. The 0.05 second vector has little or no change from its previous position in group I. Again, a few open loops are seen in all three planes.

GROUP III: (THIRTEEN MONTHS TO FIFTEEN YEARS)

Thirteen Months to Three Years: In the horizontal plane there were three figure of eight patterns. While the 0.02 and 0.03 second vectors were directed to the left, anteriorly and inferiorly, the 0.04 second vector had now shifted mostly to the left, posteriorly and inferiorly. In addition, a few 0.05 second vectors were seen pointing to the left, posteriorly and inferiorly.

Three to Six Years: There were three figure of eight patterns in the horizontal plane. The 0.04 second vector was exclusively to the left, inferiorly and posteriorly and, occasionally, anteriorly. The 0.05 second vector continued to shift more to the left, posteriorly and inferiorly. The 0.02 and 0.03 second vectors remained the same and no further change was seen in the older age groups, except for slight leftward shift but still maintaining their anterior orientation.

Six to Ten Years: There were also three figure of eight patterns in the horizontal plane. The last figure of eight was seen in one patient at eight years. The 0.05 second vector was now oriented exclusively to the left, posteriorly and inferiorly. Frequently it pointed superiorly. Furthermore, the 0.05 second vector was now farther away from the E point.

Ten to Fifteen Years: There were no figure of eight loops in this subgroup. All loops appeared to be normal adult patterns. There were no open loops in all three planes.

Comment: Counterclockwise rotation in the horizontal plane is evident in this group. The last trace of figure of eight pattern is seen in the subgroup from six to ten years. Complete adult pattern, characterized by counterclockwise rotation in the horizontal plane and a more posteriorly oriented loop, is present in the last subgroup from eleven to fifteen years. The change in the orientation of the 0.04 and 0.05 second vectors is an important hallmark that separates this group from the previous groups I and II. All loops are closed.

SERIAL TRACINGS

The six patients with serial vectorcardiograms showed different ages of onset and termination of the "transition" period. The earliest "transition" was seen in one patient at age ten days and the "transition" was completed in a very short time at twenty-one days of age. The latest onset in this group was at six weeks and the latest completion was at seven months. Figure 2 shows the progressive changes in the serial QRS vectorcardiograms of a patient from age eight days to age fifteen weeks as seen in the horizontal plane.

Comment: The wide variation in time of onset and termination in the "transition" period of these six patients may in part explain the difficulty of differentiating pathologic from "physiologic" right ventricular hypertrophy in this age group. A correlation of the standard height and weight with serial vectorcardiograms of normal subjects may delimit this variability to a certain extent and possibly predict the progression of the vector loop in its development to a normal adult pattern.

Figure 3 is a scattergram of the 0.02, 0.03, 0.04 and 0.05 second vectors plotted in the horizontal plane of groups I, II and III. The arrows represent in a schematic way the direction of the corresponding vectors.

COMMENTS

The division of the cases into three large age groups from birth to fifteen years was arrived at after all the data were compiled. The rapid changes in the vector loop both in morphology and rotation in the first months of postnatal life prompted us to subdivide group I (birth to one month) into smaller age groups of: birth to seven days, eight to fourteen days and fifteen days to one month. After the first month the changes consist in the transformation of the loop into the figure of eight pattern or in the process of unwinding. This approximately spans the period of group II from five weeks to one year, inclusive. Group III includes all patients from one to fifteen years. The changes in this period are much slower than in the previous two groups, consisting mainly in a posterior displacement of the loop with increasing age. Counterclockwise rotation in the horizontal plane is invariably present.

The observations of Keen[11] in his study of the postnatal development of the human ventricles from birth to sixteen years, inclusive, ade-

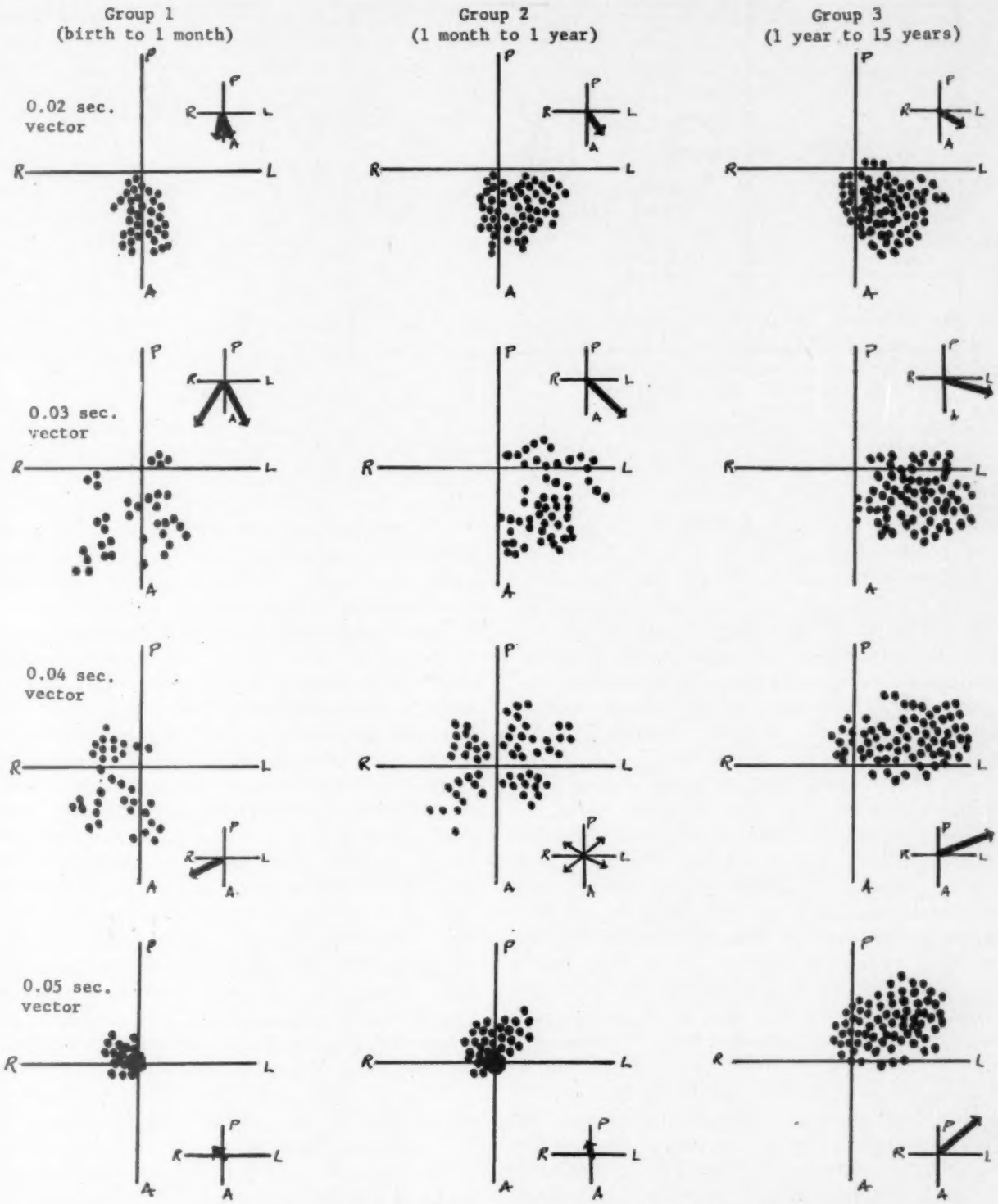

FIG. 3. Scattergram of 0.02, 0.03, 0.04 and 0.05 second vectors plotted in the horizontal plane.

quately justify this age grouping. He found a rapid change in the ratio between the right and left ventricular mass amounting to about 75 per cent during the first month of life. Thereafter, a slower change in this ratio takes place until the age of six months. From then on the ratio between the right and left ventricle consistently assumes adult proportions. These rapid changes in ratio are made possible by right ventricular atrophy accompanied by a rapid increase in the left ventricular mass during the first months of life. The right ventricle

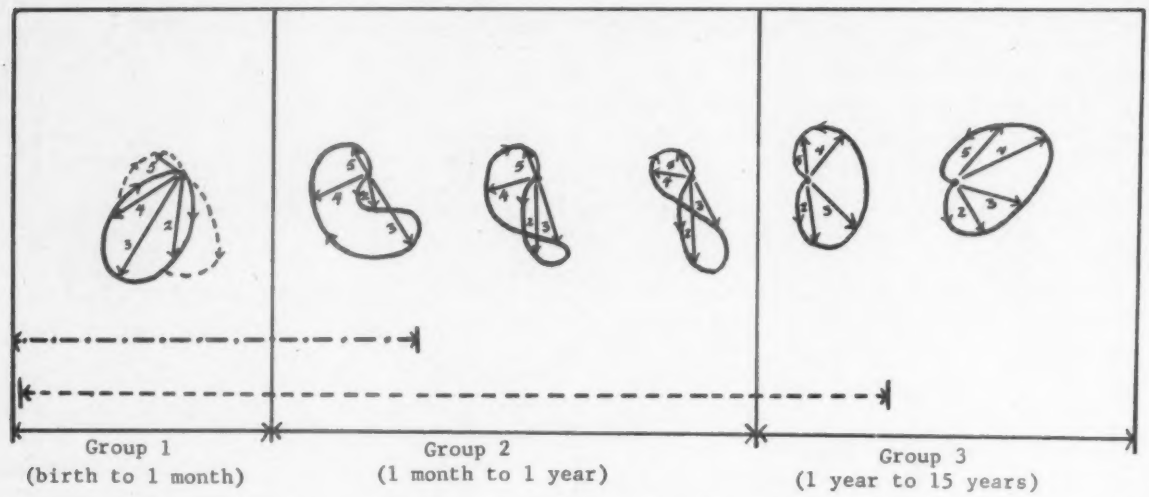

FIG. 4. Progression of the vector loop from birth to fifteen years (horizontal plane). ·-·-·-·-·-·- = range of clockwise rotation (0–4 mo.); - - - - - - = range of "transition" period (neonatal period to 10 years); 2, 3, 4, 5 represent 0.02, 0.03, 0.04 and 0.05 second instantaneous vectors, respectively.

does not regain its weight at birth until the first year of life is reached.

According to Elek et al.[3] the loop is located in the right anterior and inferior quadrant in the first month of life. Our findings do not bear out this assumption. We found a wide range of variation as did Rosen and Gardberg[7] in their study. The 0.02 and 0.03 second vectors, although exclusively oriented anteriorly, may point either leftward or rightward. Figure of eight patterns may start to appear in the first three days of life.

The "transition" period is extremely variable, either in onset or termination. Roughly, the whole "transition" period is delimited by the neonatal period and the end of the first decade. Although most of this period is encompassed by group II (five weeks to one year), the boundaries at both ends are not sharply defined. The tracings of the six patients who had serial vectorcardiograms through their "transition" indicate that the duration of the "transition" period can be as short as two weeks and as long as five to six months. Actually, the presence of figure of eight patterns past five to six months in group II exclusive of these six patients may mean longer periods of "transition." Perhaps it can be safely said that the normal "transition" period does not go beyond the first decade of life. Elek et al.[3] noted a figure of eight pattern in a thirty-eight year old patient with "incomplete right bundle branch block" in the electrocardiogram. Lamb and Dimond[2] state that a figure of eight in the horizontal plane is uncommon in a normal adult over the age of twenty years. We did not find any figure of eight in the horizontal plane in the twenty-one patients included in the subgroup from ten to fifteen years.

From birth to one year the duration of the QRS loop is about 0.45 to 0.58 second. The rapid changes of the QRS loop in the first month are best depicted by the 0.02 and 0.03 second instantaneous vectors. A change from right to left anterior takes place in the first month with these vectors. After the third month the 0.02 second vector is exclusively to the left of the E point, directed anteriorly or posteriorly and inferiorly. The 0.02 second vector may shift somewhat to the right as the centrifugal limb of the figure of eight becomes more anterior than the centripetal limb. Accompanying this change in the 0.02 and 0.03 second vectors, the loop reverses its rotation from clockwise to counterclockwise. Approximately at the fourth month, all loops have assumed counterclockwise rotation in the horizontal plane.

After the first year the QRS progressively widens until it reaches the adult dimension at ten to fifteen years. With the widening of the QRS loop, the 0.04 and 0.05 second vectors begin to shift to the left. The 0.02 and 0.03 second vectors remain in anterior, inferior and directed to the left. The 0.04 second vector starts to shift to the left, posteriorly and inferiorly soon after the first year and completes the movement to this quadrant at three to six years. The 0.05 second vector follows closely the migration of the 0.04 second vector to the same quadrant. At ten to fifteen years a normal

adult pattern is uniformly present and the QRS loop measures about 0.08 second. All loops are closed, all are rotated counterclockwise in the horizontal plane, and all clockwise in the sagittal, and either clockwise or counterclockwise in the frontal.

The progression of the QRS loop in the horizontal plane from birth to fifteen years is the most informative in the cube system. It epitomizes the broad spectrum of a rapidly changing vectorcardiogram covering the whole period of infancy and childhood in an uninterrupted fashion. These progressive changes are represented in a schematic way in Figure 4. In this diagram, the range of clockwise rotation and the "transition" period is purposely extended to four months and ten years, respectively, although the latest examples of each are at three months and eight years in this series. Further studies are needed to delineate a sharper demarcation line for these two parameters.

Summary

One hundred sixty-six QRS vectorcardiograms from 154 patients with normal hearts have been analyzed according to morphology and rotation of the loop and position of the 0.02, 0.03, 0.04 and 0.05 second instantaneous vectors. The patients' age ranged from birth to fifteen years inclusive. The vectorcardiograms were taken with an apparatus similar to that of Shillingford and Brigden using the cube system of Grishman.

Variations in the morphology and rotation of the QRS loop are not uncommon in the first month of life. The "transition" period has also considerable variation as to the time of onset and termination. As a rule, in the horizontal plane of the cube system, counterclockwise rotation should be seen at four months and the figure of eight pattern should be absent at ten years in a normal vectorcardiogram. At three months and over, the 0.03 second instantaneous vector normally should not be directed to the right.

The horizontal plane of the cube system of Grishman gives the most information relative to the progressive changes in the QRS loop from birth to fifteen years.

Acknowledgment

We are indebted to Drs. O. W. Hosterman and W. E. Wheeler and to Miss Ina Fritz of Children's Hospital, Columbus, Ohio, for taking all the vectorcardiograms used in this study.

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The Vectorcardiogram in Direct Posterior Wall Myocardial Infarction*

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THE vectorial concept of the electrical activity of the heart implies that when myocardial infarction occurs, the involved fibers are rendered electrically inert, and the early forces of the QRS loop are directed away from the inert area. Since the electrical forces generated by depolarization of the posterior wall of the left ventricle are directed to the left and posteriorly, it may be assumed that infarction of this area would result in abnormal early forces oriented to the right and anteriorly.[1,2] This would cause prominent R waves in right precordial leads of the scalar electrocardiogram, but would produce no characteristic changes in the extremity leads since the altered forces are directed perpendicular to the frontal plane. Unfortunately, increased amplitude of the R wave in right precordial leads may not be recognized as indicative of myocardial infarction and may be incorrectly interpreted as evidence of right ventricular hypertrophy or right bundle branch block.

The purpose of this report is to demonstrate the value of the vectorcardiogram in establishing the diagnosis of direct posterior wall infarction and in distinguishing it from other causes of prominent R waves in right precordial leads.

MATERIAL AND METHODS

Vectorcardiograms have been obtained in eighty-four patients with myocardial infarction. In six cases the early QRS forces were abnormally displaced to the right and anterior. All of these had definite clinical and laboratory evidence of myocardial infarction including characteristic serial serum transaminase changes. One case was confirmed by necropsy. There was no clinical or roentgenologic evidence of pulmonary infarction, chronic pulmonary disease or right ventricular hypertrophy in any of the six patients.

Vectorcardiograms were obtained with a Sanborn vectorcardiograph employing the cube reference system.[3] Electrocardiograms, including standard and unipolar extremity leads and routine precordial leads, were recorded with a Sanborn electrocardiograph.

CASE REPORTS

CASE *1.* A fifty-seven year old white man was admitted to the hospital on March 23, 1960, with complaints of crushing substernal pain, nausea and dizziness of four hours' duration. Physical examination revealed a blood pressure of 140/70 mm. Hg and sinus bradycardia of 52 per minute. The heart sounds were distant, but no other abnormalities were noted. The serum glutamic oxaloacetic transaminase (SGO-T) obtained one hour after hospitalization was 115 units (normal, 40 units). He was treated with opiates, oxygen and anticoagulants. Despite large doses of morphine, his substernal pain persisted. On March 25, 1960 he suddenly expired approximately forty-eight hours after admission.

The electrocardiogram taken at the time of hospitalization on March 23, 1960 (Fig. 1A) shows deep Q waves and striking elevation of the S-T segments in leads II, III and aVF. There is marked depression of the S-T segments in precordial leads V_1, V_2 and V_3. Twenty-four hours later (Fig. 1B), there are deep Q waves with less elevated S-T segments and inverted T waves in leads II, III and aVF. The QRS complex in aVR is now upright. Prominent R waves are seen in leads V_1 and V_2, and the S-T segment is isoelectric in the right precordial leads. The T wave is inverted in leads V_5 and V_6. In the *vectorcardiogram* taken on March 24, 1960 (Fig. 1C), the entire QRS loop is displaced anteriorly and superiorly. The initial QRS forces are abnormally oriented to the right, anterior and superior.

Postmortem examination revealed 300 cc. of liquid and clotted blood in the pericardial cavity. A 7 by 5.5 cm.

* From the Charles Block Cardiac Research Laboratory, Newark Beth Israel Hospital, Newark, New Jersey. This study was supported in part by U. S. Public Health Service Research Grant HF-8685.

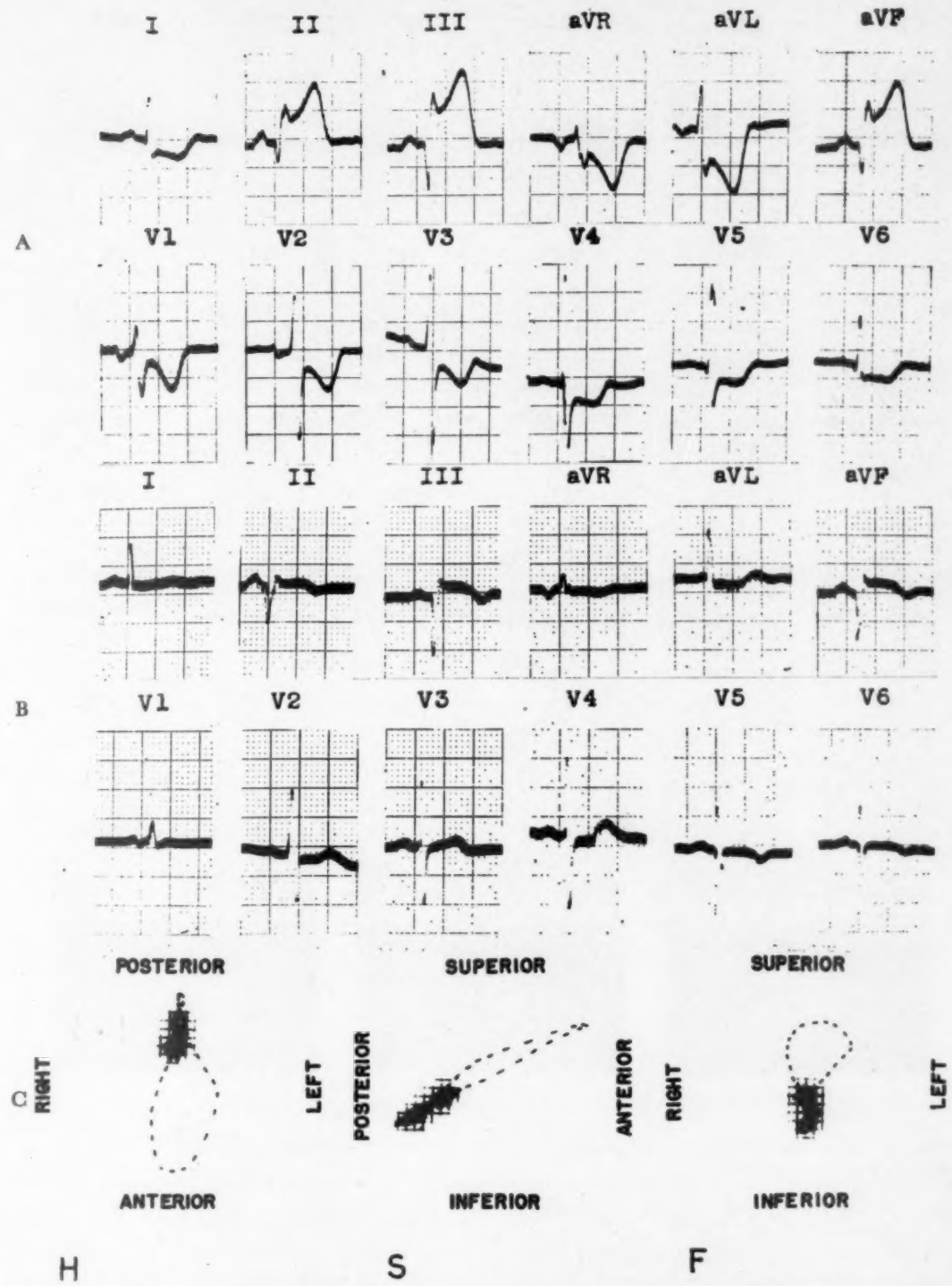

FIG. 1. Case 1. A, electrocardiogram of March 23, 1960. B, electrocardiogram of March 24, 1960. C, vectorcardiogram of March 24, 1960. H, S and F indicate horizontal, sagittal and frontal planes.

recent transmural infarct involving most of the inferior and posterior surfaces of the left ventricle was noted. In the center of the infarcted area, a 0.1 cm. defect was seen through which a probe could be readily passed into the left ventricular cavity. A fresh thrombus was observed occluding the right coronary artery, approximately 3.5 cm. from it ostium.

Comment: The initial electrocardiogram indicated an inferior or diaphragmatic wall infarction. The second record showed additional

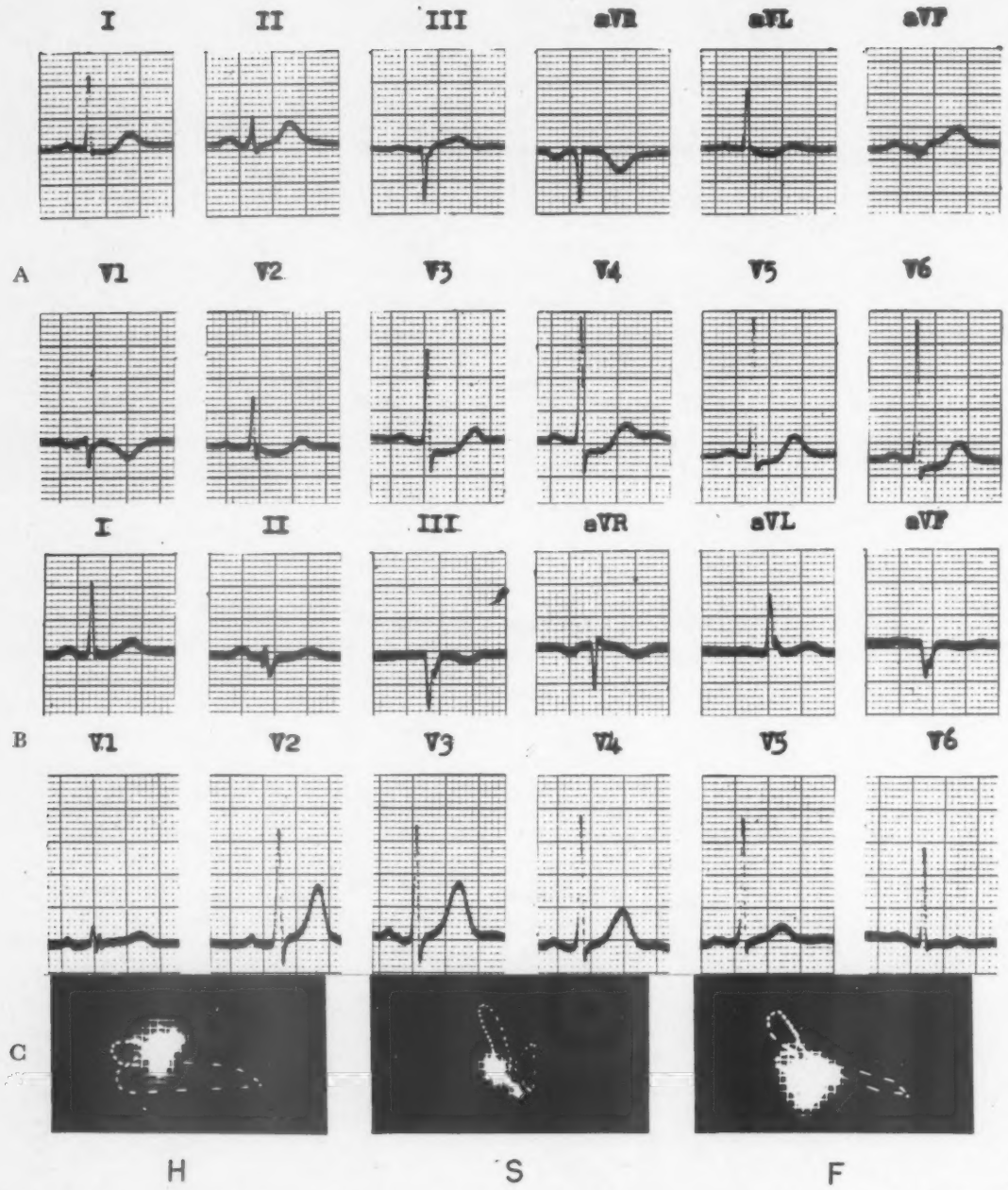

FIG. 2. Case 2. A, electrocardiogram of January 12, 1959. B, electrocardiogram of February 10, 1959. C, vectorcardiogram of February 10, 1959.

findings of prominent R waves in leads V_1, V_2 and aVR, and the vectorcardiogram confirmed the presence of QRS forces which were abnormally oriented to the right and anterior as well as superior. These findings were interpreted as indicating direct posterior as well as inferior infarction and this was confirmed by autopsy.

CASE 2. A fifty-nine year old white male physician was admitted to the hospital on January 12, 1959 following a three day history of increasingly severe interscapular pain radiating down both arms and anteriorly to the substernal area. The physical examination was abnormal only in that the heart tones were nearly inaudible. The white cell count was 12,000 per cu. mm., the sedimentation rate was 86 mm. in one hour, and the SGO-T was 95 units. The pain subsided about two days after admission, and he was discharged on February 11, 1959 after an uneventful recovery.

The electrocardiogram at the time of admission to the hospital (Fig. 2A) shows S-T segment depressions in leads I, aVL, V_2 to V_6. The QRS complex in V_1 is rS in configuration. In the tracing taken four weeks later (Fig. 2B), there is a shallow Q wave in

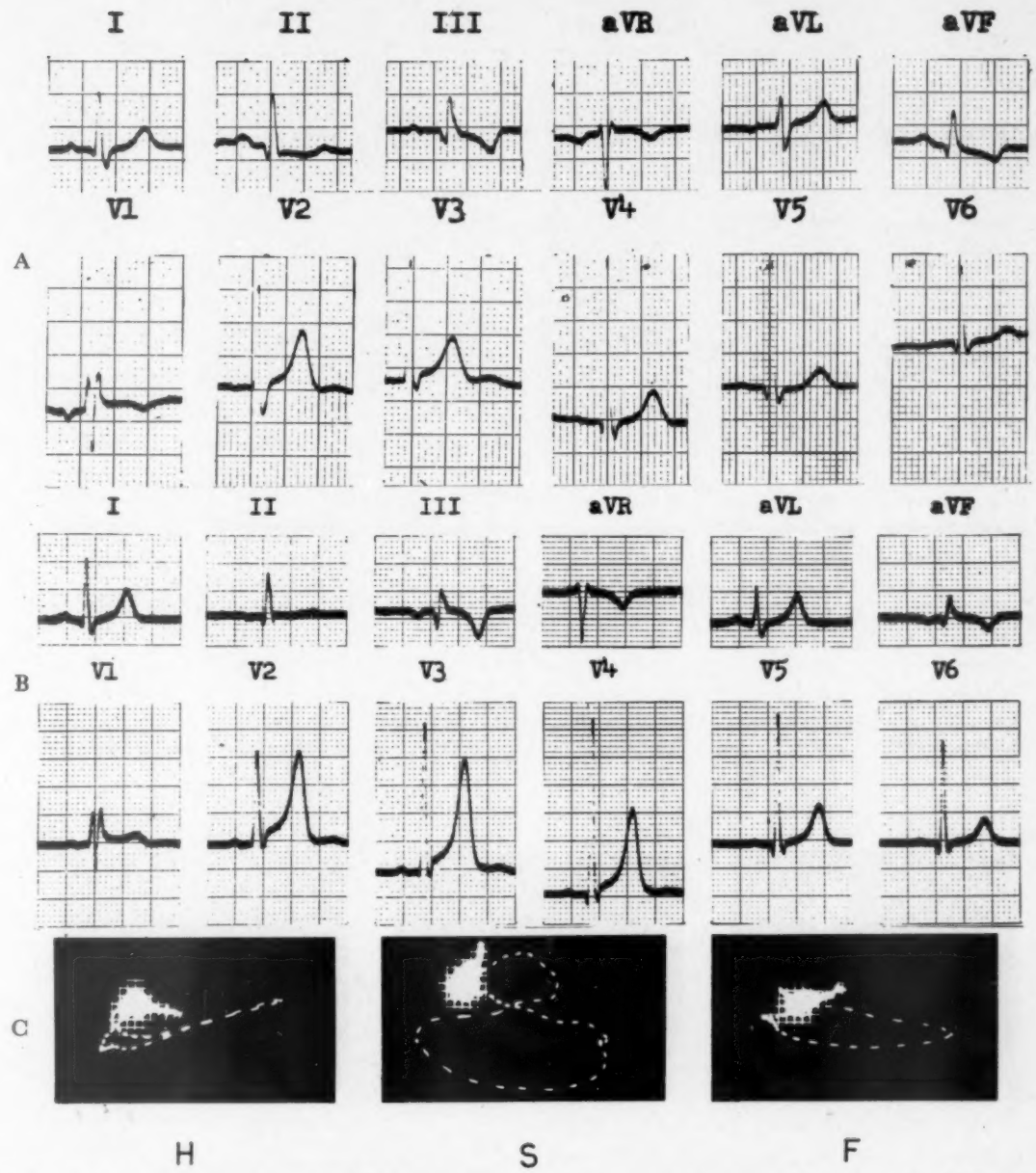

Fig. 3. Case 3. A, electrocardiogram of February 8, 1959. B, electrocardiogram of February 15, 1959. C, vectorcardiogram of February 15, 1959.

lead II, and a deep QS in leads III and aVF. The T wave is flat to inverted in these leads. The R wave is tall in V_2 and V_3 and RSR′ complex is present in V_1. The T wave is now upright in V_1 and is upright and peaked in V_2 and V_3. In the *vectorcardiogram* (Fig. 2C) obtained with the second electrocardiogram, both the initial and terminal QRS forces are displaced to the right, anterior and superior. Nearly the entire QRS loop is oriented anteriorly and superiorly.

CASE *3.* A sixty-five year old white man with a history of angina pectoris on effort was hospitalized on February 7, 1959 following a bout of prolonged precordial pain. Initial physical examination was not remarkable. The SGO-T was obtained ninety-six hours after onset of chest pain and was only slightly elevated. He complained of almost constant substernal distress until February 12, 1959 when the pain became mild and recurred infrequently.

The electrocardiogram obtained twenty-four hours after admission (Fig. 3A) shows a Q wave in leads II, III and aVF and an inverted T wave in leads III and aVF. In V_1 there is an RSR′ complex with an inverted T wave. A tracing taken one week later (Fig. 3B) shows an RSR′ complex in V_1 with an upright T wave, and prominent R waves with tall, peaked T waves in V_2, V_3 and V_4. In the accompanying *vectorcardiogram* (Fig. 3C), the initial QRS forces are abnormally displaced to the right, anterior

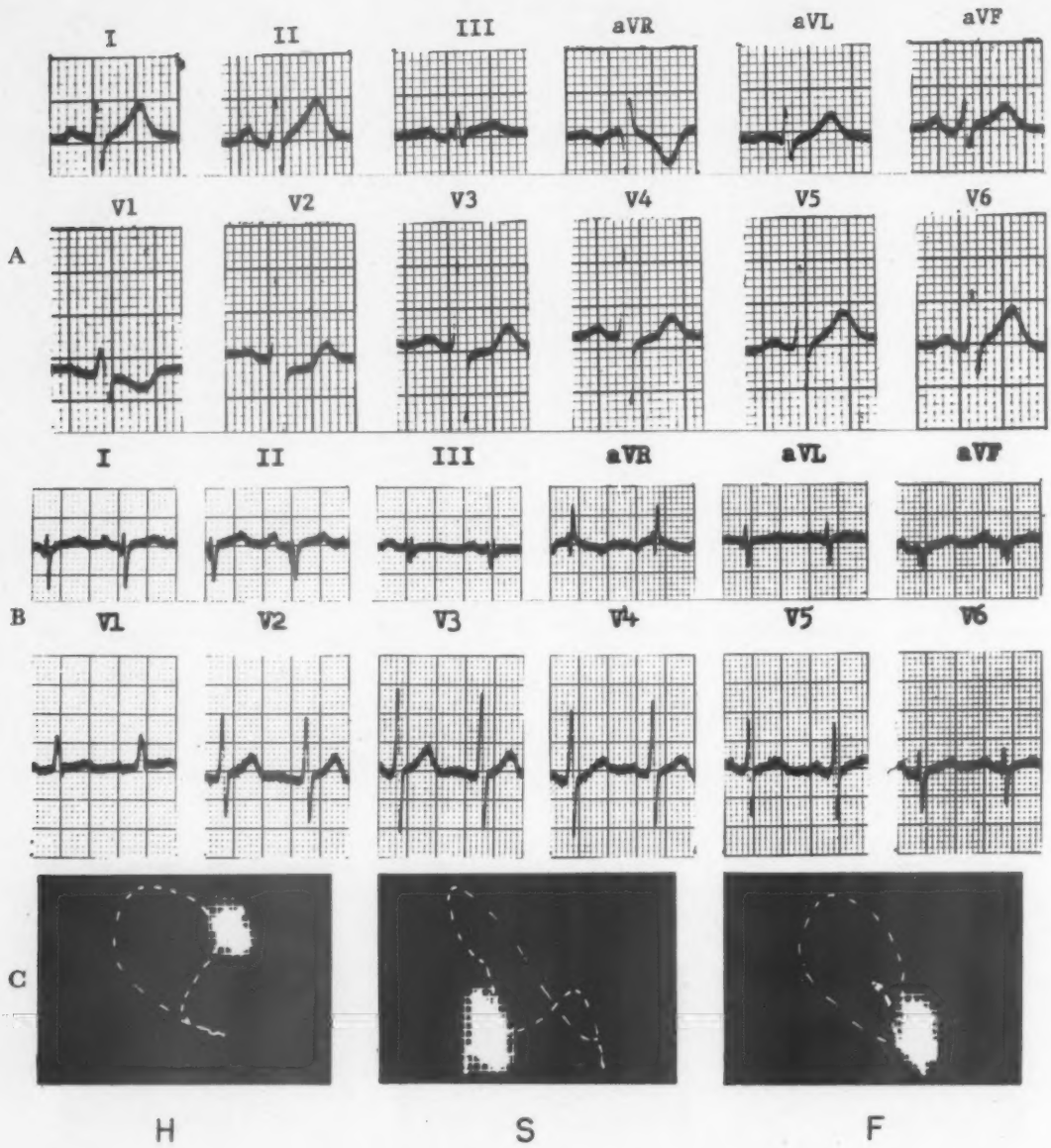

FIG. 4. Case 4. A, electrocardiogram of April 2, 1957. B, electrocardiogram of September 20, 1958. C, vectorcardiogram of September 20, 1958.

and superior. The terminal forces are directed to the right and anterior, and there is marked anterior orientation of most of the QRS loop.

Comment: RSR′ complexes are seen in lead V_1 of Cases 2 and 3. These might be interpreted from the scalar electrocardiogram as an atypical form of right bundle branch block. The vectorcardiogram, however, reveals no evidence of terminal conduction delay, but shows that this peculiar morphology is caused by posterior infarction, resulting in anterior and rightward orientation of initial and terminal forces with the midportion of the QRS loop directed to the left.

CASE *4.* A forty-five year old white man was admitted in shock on April 1, 1957 following an episode of sudden precordial pain. He had been aware of exertional angina relieved by rest for one year prior to hospitalization. He appeared moribund initially but slowly responded to mephentermine, oxygen and analgesic therapy. There was no evidence of phlebitis or pulmonary infarction. Two chest x-ray films taken one week apart were normal. Following clinical improvement, he was discharged on April 25, 1957. On September 20, 1958, approximately seventeen months after discharge, he was seen again. There was no intervening history of chest pain, cough, dyspnea or phlebitis. Pulmonary function studies including ventilation volumes and arterial oxygen saturation before and after exercise

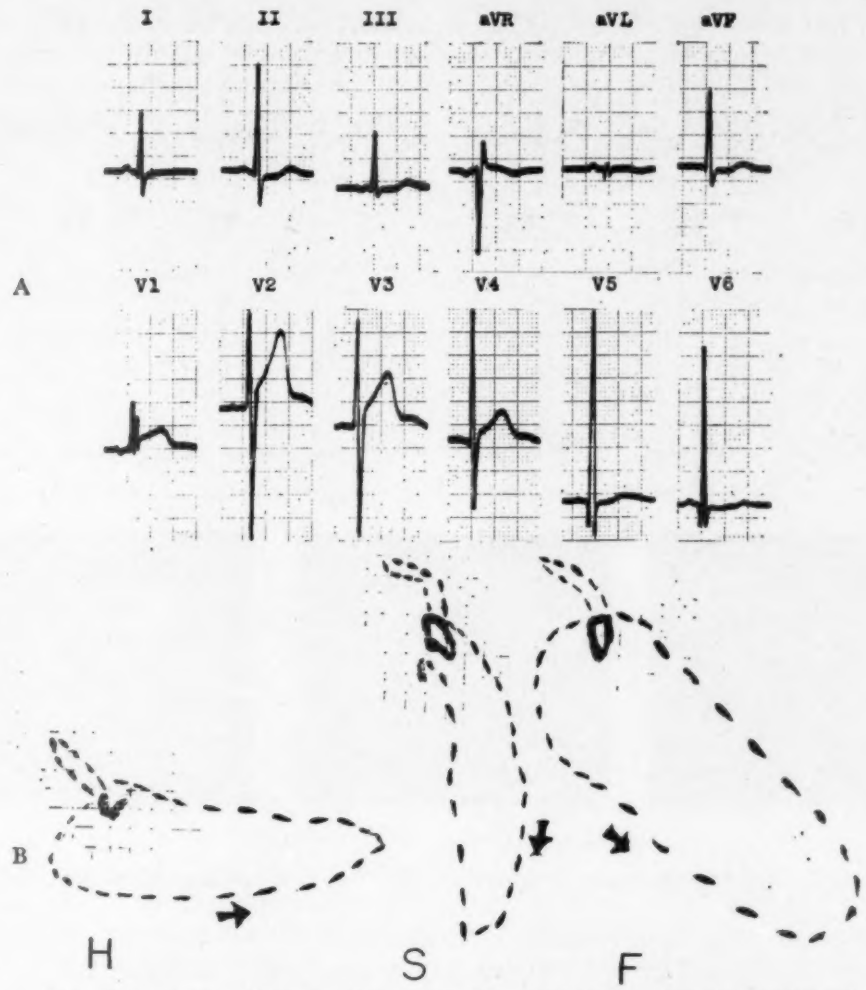

FIG. 5. Case 5. A, electrocardiogram of March 22, 1958. B, vectorcardiogram of March 22, 1958.

were within normal limits. Right heart catheterization also performed at that time revealed a normal right ventricular pressure of 18/0 mm. Hg.

The electrocardiogram obtained on the second hospital day (Fig. 4A) displays an equiphasic RS complex and an inverted T wave in V_1 with slight depression of the S-T segment in V_1 to V_4. Seventeen months later (Fig. 4B), there are predominantly negative QRS complexes in I and aVL, an RSR′ configuration in aVR with embryonic R waves followed by deep S waves in II, III and aVF. In V_1 there is a prominent, slurred R wave and an upright T wave, while the complex in V_6 is RS in type. The simultaneous *vectorcardiogram* (Fig. 4C) shows the entire QRS loop to be oriented to the right, anterior and superior with clockwise direction of inscription in the horizontal plane. The early QRS forces are delayed and follow a circuitous pathway.

Comment: This case demonstrates the difficulty in distinguishing posterior infarct from right ventricular hypertrophy in the routine electrocardiogram. The vectorcardiogram in posterior infarct also resembles that obtained in right ventricular hypertrophy since the QRS loop is displaced to the right and anterior and is sometimes inscribed in a clockwise direction in the horizontal plane as in Figure 4C. However, in posterior infarct the initial forces show delay in inscription and abnormal contour probably related to peri-infarction conduction disturbance.

CASE *5.* A thirty-two year old white man noted the sudden onset of crushing substernal pain on March 12, 1958. He was admitted to the hospital about four hours after the pain began when he was observed to be ashen grey and markedly diaphoretic. The blood pressure was 160/100 mm. Hg, and the ventricular rate was 100 per minute. The heart sounds were distant and fine rales were heard at the right base posteriorly. About forty-eight hours later, the pain subsided and the breath sounds were normal. The SGO-T was 187 units on the second hospital day and 62 units two days later. He was discharged asymptomatic on April 24, 1958.

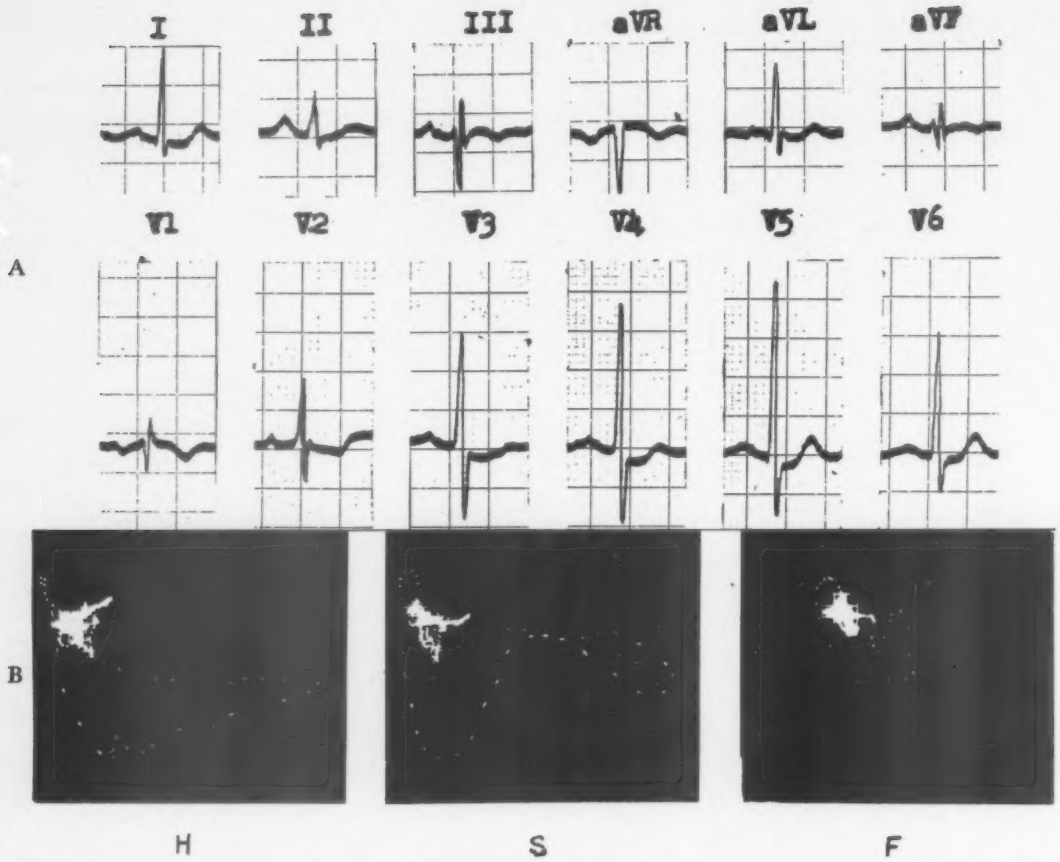

FIG. 6. Case 6. A, electrocardiogram of March 26, 1959. B, vectorcardiogram of March 26, 1959.

The electrocardiogram ten days after the onset of chest pain (Fig. 5A) shows flat T waves in leads I and aVL. There is a prominent M-shaped complex in V_1 with an upright T wave. The QRS voltage is large in the other precordial leads with flat T waves in V_5 and V_6. In the *vectorcardiogram* (Fig. 5B), the entire QRS loop is displaced anteriorly, and the initial forces are abnormally oriented to the right and anterior.

CASE *6.* A seventy-two year old Negro woman was seen on March 25, 1959 with a complaint of three severe, prolonged bouts of precordial pain radiating to the left shoulder in the preceding twenty-four hours. She admitted to frequent exertional angina pectoris in the past two years. The physical examination revealed only systemic hypertension of 190/110 mm. Hg. The SGO-T on March 25, 1959 was 124 units which then diminished to 84 units on March 26, 1959 and 39 units twenty-four hours later.

The electrocardiogram of March 26, 1959 (Fig. 6A) reveals slight depression of the S-T segment in leads I and aVL. There is an RSR′ complex in V_1 and a rather prominent R wave in V_2. The S-T segment is depressed in leads V_3 to V_6. In the corresponding *vectorcardiogram* (Fig. 6B), the entire QRS loop is displaced anteriorly with rightward and anterior orientation of the initial forces which are inscribed with considerable delay and abrupt directional changes. The QRS loop is written in a clockwise direction in the horizontal plane.

Comment: In the first four cases, there was evidence of combined posterior and diaphragmatic infarction. When the lesion is localized to the posterior wall as in Cases 5 and 6 the routine electrocardiogram will not show the characteristic pattern of myocardial infarction. In these instances, however, the QRS loop in the vectorcardiogram is abnormally displaced anteriorly and to the right.

COMMENTS

The posterior wall of the left ventricle lies infra-atrially and extends superiorly, posteriorly and laterally facing partially toward the left shoulder. It should be distinguished from the inferior or diaphragmatic surface where infarction has been designated as "posterior infarct." Involvement of the latter area causes characteristic changes in leads II, III and aVF whereas in true posterior infarction, the altered forces are directed perpendicular to the frontal plane thereby causing no abnormalities in the extremity leads. Previous postmortem studies[4–6] have shown that direct posterior wall infarctions

are characterized by tall R waves in right precordial leads. However, Dunn et al.[7] remarked that "alteration in the height of a normally occurring R wave may not be particularly helpful in establishing the presence of myocardial infarction." These authors added that "vectorcardiographic study of this disturbance in the normal balance of electric forces may afford a means of using the phenomenon to greater diagnostic advantage."

The vectorcardiograms obtained in this study clearly demonstrate the genesis of the findings in the scalar electrocardiogram in posterior wall infarction. When infarction involves this portion of the left ventricle, normally directed posterior and leftward forces are lost, and a new balance of forces is created displaced anteriorly and to the right. This results in increased prominence of the R waves in right precordial leads of the scalar electrocardiogram.

Previous reports have described depressed S-T segments and peaked, upright T waves in right precordial leads of patients with posterior infarction.[4-6, 8-10] These represent injury and ischemia of the posterior wall and are a mirror image of the classic pattern of infarction which would be seen in posterior chest leads in such cases. Marked S-T segment depressions in right precordial leads signifying acute posterior injury are seen in Case 1 (Fig. 1A). In Cases 2 and 3 there are peaked, upright T waves in right precordial leads, while previously flat or inverted T waves in these leads became positive following infarction in Cases 1 and 4.

Since both the diaphragmatic and posterior surfaces of the left ventricle usually receive their blood supply from the right coronary artery, infarction of both areas is likely to occur simultaneously as seen in the first four cases. Complicating diaphragmatic infarction in these cases is indicated by the classic changes in extremity leads II, III and aVF and abnormal superior orientation of the early forces of the QRS loop in the vectorcardiogram. When infarction is restricted to the posterior wall as in Cases 5 and 6, the routine electrocardiogram may not be helpful since relative changes in R wave height in right precordial leads are difficult to evaluate. However, in these cases, the vectorcardiogram clearly demonstrates the anterior and rightward displacement of the QRS loop with delay in inscription and abnormal contour of initial force that we consider diagnostic of posterior wall infarction.

Differentiation From Right Bundle Branch Block and Right Ventricular Hypertrophy: RSR′ complexes are seen in lead V_1 of Cases 2, 3 and 6. These might be interpreted as an atypical form of right bundle branch block. However, the vectorcardiogram reveals no evidence of terminal conduction delay but shows that this peculiar morphology is due to anterior and rightward orientation of initial and terminal forces with the midportion of the QRS loop directed to the left.

Posterior wall infarction must also be differentiated from right ventricular hypertrophy since both may cause prominent R waves in right precordial leads. Vectorcardiographically, posterior wall infarction may simulate right ventricular hypertrophy in that in the horizontal plane the QRS loop is oriented to the right and anterior and may even be inscribed in a clockwise direction (Figs. 4C and 6B) as seen characteristically in right ventricular hypertrophy. However, in posterior infarction the initial forces show delay in inscription and bizarre contour presumably due to peri-infarction conduction disturbance. This finding is not seen in uncomplicated right ventricular hypertrophy.

Summary

1. Employing the cube reference system, vectorcardiograms were obtained in six cases of myocardial infarction involving the posterior wall of the left ventricle.

2. In these vectorcardiograms, the early forces of the QRS loop were abnormally displaced anteriorly and to the right. This finding accounts for the increased R wave amplitude in right precordial leads of the scalar electrocardiogram that is seen in posterior wall infarction.

3. The vectorcardiogram is of particular diagnostic value when infarction is localized to the posterior surface since the classic pattern of myocardial infarction is not evident in the routine electrocardiogram.

4. Vectorcardiography serves to differentiate posterior infarct from other causes of prominent R waves in right precordial leads such as right bundle branch block and right ventricular hypertrophy.

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The Vectorcardiogram in Dorsal or Posterior Myocardial Infarction*

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THE ELECTRICAL EVENTS that occur following myocardial infarction can be represented by three principal vectors; namely, those of necrosis, injury and ischemia.[1,2] Owing to their particular electrogenesis,[1] the vectors of necrosis and ischemia point "away" from the infarcted area, thus permitting the inscription of deep Q waves and negative T waves in the leads that "face" the site of infarction. At the beginning of the coronary accident, a positive displacement of the S-T segment can be registered in those leads as the result of a current of injury represented by a vector pointing "toward" the infarcted zone.

The spatial orientation of these vectors depends on the site of infarction. Thus, in infarction of the inferior or diaphragmatic wall of the heart these vectors are parallel to the frontal plane; the vectors of necrosis and ischemia will point upward and the vector of injury downward. When the infarction is located in the anteroseptal wall the vectors are oriented almost perpendicularly to the frontal plane and parallel to the horizontal plane; the vectors of necrosis and ischemia point backward and that of injury forward. This orientation determines the inscription of Q waves, positive S-T displacement and inverted T waves in the right precordial leads. When the infarction is located in the posterior[1] or dorsal[3] wall the vectors, although parallel to the horizontal plane, are oriented in the opposite direction; the vectors of necrosis and ischemia point forward and that of injury backward (Fig. 1).

We must emphasize that the exact position of the "dorsal wall of the heart" in the living subject does not seem clear.[3] This wall of the left ventricle below the A-V sulcus is oriented to the back of the body and should not be confused with the inferior or diaphragmatic wall which erroneously has been called the "posterior" wall by many authors.

Electrocardiographically, infarction located in the dorsal wall is considered relatively rare.[3] There are only a few references[4–7] in vectorcardiography to the electrical events of some cases of infarction of the true posterior or posterolateral wall of the left ventricle.

MATERIAL AND METHODS

In the present study the vectorcardiograms of twenty-five male patients with what we considered old dorsal or true posterior infarction were analyzed; in one case the vectorcardiogram was also obtained during the acute phase of the coronary accident (Fig. 2 and 3). All patients revealed the typical clinical picture of myocardial infarction, confirmed by laboratory and follow-up data. The patients' ages ranged from thirty-three to sixty-five years, the average being fifty-three years.

Vectorcardiograms were obtained with Grishman's cube system,[8] with simultaneous inscription of the components of the cube and electrocardiogram leads by a four-channel Sanborn Polyviso apparatus. The vectorcardiographic loop was modulated to indicate the sense of rotation and was interrupted 400 times per second. Based on the orientation of the initial portions (0.02 second) of the QRSsÊ and the presence of abnormal Q waves in the A (right-left) and C (superior-inferior) components of the cube, our patients were classified into four groups according to the area of myocardial necrosis. All groups had tall R waves in the B (anterior-posterior) component.

CLASSIFICATION

The four groups classified according to area of necrosis were as follows:

1. *Strictly dorsal infarction,* showing only an increase of the R waves in the B component [three

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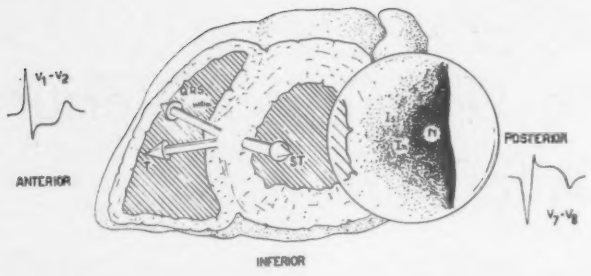

FIG. 1. Orientation of the vectors of necrosis, injury and ischemia in an infarct of the dorsal region of the heart, with the typical electrocardiogram of anterior and posterior chest leads.

cases, one of which was complicated by complete right bundle branch block (Fig. 4)].

2. *Inferodorsal infarction*, showing abnormal Q waves in the C component [five cases (Fig. 5)].

3. *Laterodorsal infarction*, showing abnormal Q waves in the A component [eight cases (Fig. 2)].

4. *Inferolaterodorsal infarction*, showing abnormal Q waves in the A and C components [nine cases, two of which were complicated by complete right bundle branch block (Fig. 6 and 7)].

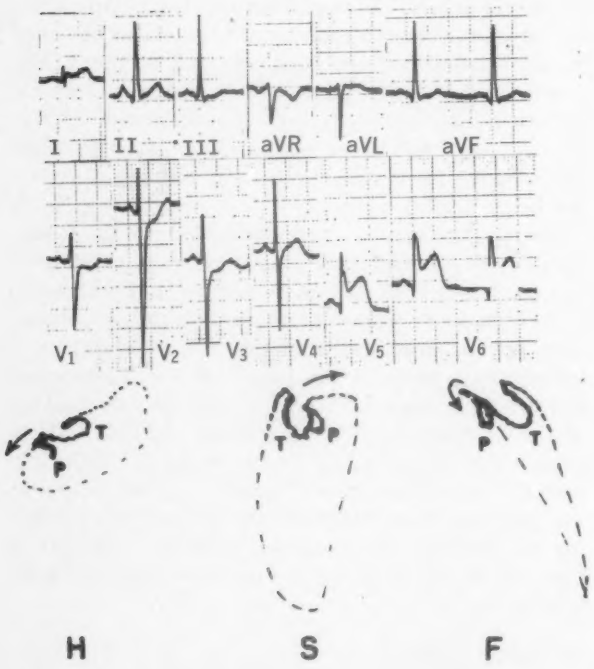

FIG. 2. Electrocardiogram and vectorcardiogram of a forty-three year old patient presenting a recent laterodorsal infarction. Note the great magnitude of the current of injury with the corresponding S-T vector oriented backward and to the left. H, S and F indicate horizontal, sagittal and frontal planes. The QRS loop shows only slight deformity and a certain delay in the activation of the terminal portions.

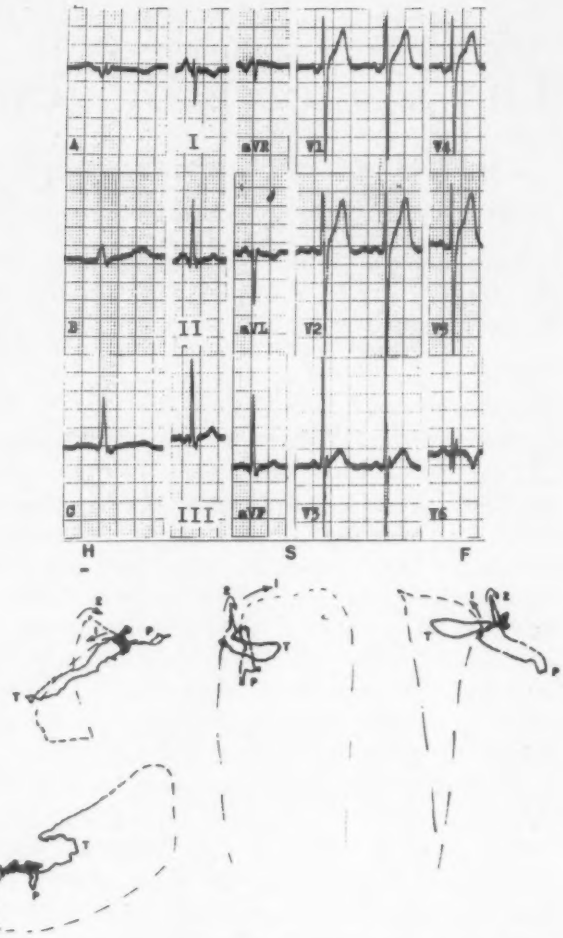

FIG. 3. Same patient as in Figure 2, five months later, with healed laterodorsal infarction. The A, B and C leads are the three component leads of the vectorcardiographic cube system, recorded at a speed of 50 mm. per second. Observe the great forward and rightward shift of the QRSsÊ and TsÊ. Note also the increase in the voltage and speed of inscription of the first portions of ventricular activation. Deformity and delay of the final portions of the QRS loops are present, best seen in the horizontal plane (H). Compare this with the amplified horizontal plane of the acute phase shown below (from Fig. 2).

RESULTS

QRSsÊ

Rotation: The rotation of the QRS loop in the horizontal plane was exclusively counterclockwise in fifteen cases. In ten cases a figure of eight was registered; in these cases the initial portion, which was predominant in all cases but one, rotated counterclockwise. In the three cases complicated by complete right bundle branch block we observed a preterminal delay after the counterclockwise initial portion indicating the conduction disturbance. There

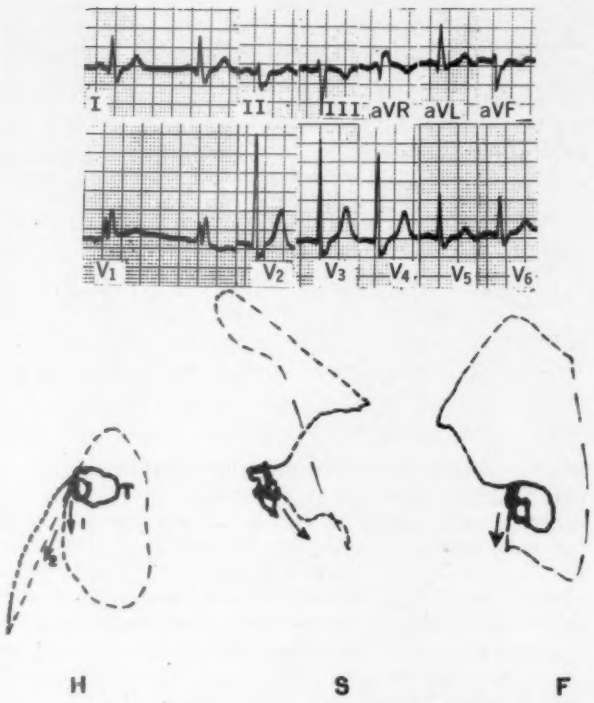

FIG. 4. Electrocardiogram and vectorcardiogram of a case of strictly dorsal infarction complicated by complete right bundle branch block. The patient, aged fifty-five, had a typical history of myocardial infarction six years before. The T wave is positive in V_1. Note the increase in magnitude of the first portions of the QRS loop, and the orientation and delay of the last portions. The TsÊ does not oppose the forces arising from the area under block, being directed to the right and anterior.

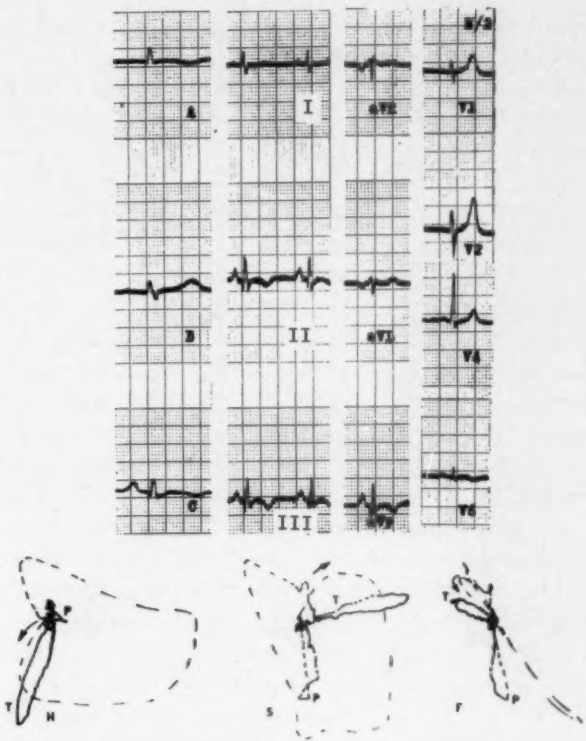

FIG. 5. Electrocardiogram and vectorcardiogram of a case of predominantly inferodorsal infarction. The ischemic area extends somewhat to the lateral wall. The patient was a fifty-eight year old man who had had coronary thrombosis four months previously. There is an increase in magnitude and speed of inscription of the first portions of the QRS loop. Note the delay and deformity of the last portions (best seen in the sagittal plane). The vector of repolarization (T loop) is directed anteriorly and points "away" from the dorsal region. This produces the tall positive T wave in V_1 and V_2.

was counterclockwise rotation in two of these cases and clockwise rotation in the other.

In the sagittal plane, there was clockwise rotation in the majority of patients (sixteen cases). In nine of them a figure of eight with a clockwise initial portion was registered.

In the frontal plane, the figure of eight configuration was observed in thirteen cases including eight presenting initial clockwise rotation. In all cases with necrosis of the diaphragmatic wall the initial portion of the QRS loop presented a clockwise rotation in the frontal plane.

Analysis of the Initial and Medial Portions: In all cases, the initial portions of the QRS loop were oriented forward and to the right. In the three cases of strictly dorsal infarction, the orientation of the initial and medial portions was predominantly forward with a duration of 0.048 second in two cases and 0.053 second in the third one. Only a small part of the initial portion was directed to the right for 0.015, 0.020 and 0.022 second, respectively.

In the five cases of inferodorsal infarcts, the initial portions of the QRS loop were directed upward and to the front. In these cases the rightward directed portion was of short duration, ranging from 0.018 to 0.025 second.

In laterodorsal infarcts (eight cases), the initial and medial portions of the QRS loop were directed mainly to the right (average duration, 0.036 second) and forward (average duration, 0.046 second). Inferolaterodorsal infarcts (nine cases) produced an upward, rightward and forward orientation of the initial portions of the QRS loop. As a whole, the rightward directed electrical forces showed durations varying from 0.015 to 0.062 second (mean value: 0.030 second) and the forward directed forces ranged in duration from 0.032 to 0.085 second (mean value: 0.048 second).

In seven cases (two of which were complicated by complete right bundle branch block),

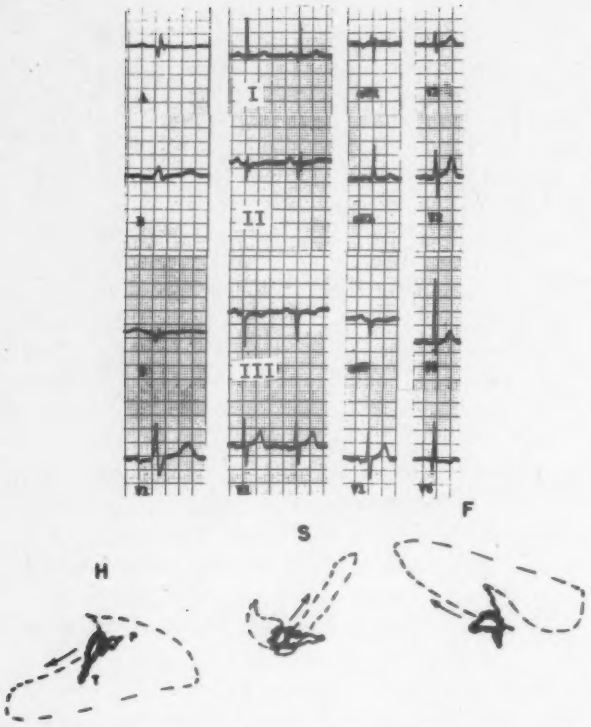

FIG. 6. Electrocardiogram and vectorcardiogram of a case of inferolaterodorsal infarction; a sixty-five year old man with a history of myocardial infarction three years previously. Note the increase in magnitude and speed of inscription of the first portions as well as the deformity and slurring of the last portions of the QRS loop. The electrical forces of depolarization are oriented predominantly forward, upward and to the right.

the first vectors were inscribed more rapidly than the normal. In five cases, a moderate or marked delay was observed in the inscription of the first portions and some initial deformity in the contour of the QRS loop was present.

Analysis of the Terminal Portions: The terminal portions were oriented backward and to the right in the majority of cases. In only six cases, including those complicated by complete right bundle branch block, were they directed forward. With relative frequency (eleven cases not complicated by complete right bundle branch block), we observed a more or less marked delay and slight deformity in the inscription of the last portions of ventricular activation.

TsÊ

The ventricular repolarization or T loop showed a backward orientation in only three cases and a forward orientation in twenty-two cases (one complicated by complete right bundle branch block). The T vector was directed to the right in ten cases and to the left in eleven cases. In four instances no lateral deviation was observed.

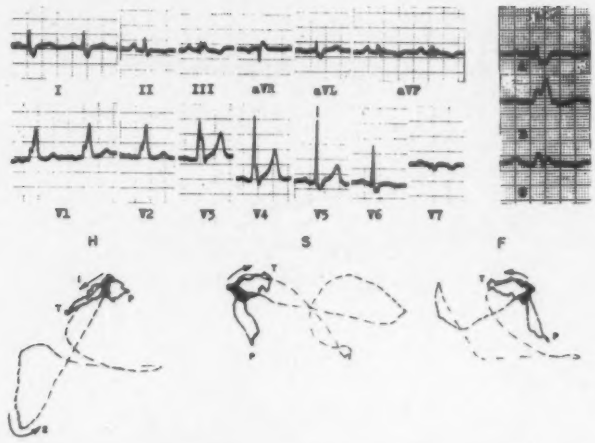

FIG. 7. Electrocardiogram and vectorcardiogram of a case of inferolaterodorsal infarction complicated by complete right bundle branch block in a fifty-four year old man who had coronary thrombosis five months previously. The T wave is positive in the right precordial leads. The TsÊ is not opposing the area under block but is pointing "away" from the infarcted region. Note the increase in the voltage and speed of inscription of the first portions of the QRS loop. Almost the entire loop is shifted forward and to the right.

COMMENTS

Vectorcardiographic Diagnosis of Dorsal Infarction: Myocardial necrosis of dorsal location is characterized in the vectorcardiogram by an increase of the initial portions (0.02 second) of the QRS loop, and a predominantly forward orientation of both the QRS and T loops. As a consequence, a tall R wave and a more positive T wave are observed in the B (anterior-posterior) component of the cube and in the right precordial leads. In cases of simultaneous involvement of areas adjacent to the dorsal region the initial portions of the QRS and T loops are directed to the right (when the lateral region is affected) or upward (when the diaphragmatic wall is affected). The diagnosis of dorsal infarct complicated by complete right bundle branch block should be made when there are signs of conduction disturbances plus an increase of the initial portions directed forward and a TsÊ tending not to oppose the orientation of the electrical forces which represent the activation of the area under block. In these cases, a relatively tall initial R wave and positive T wave can be present in the right precordial leads.

Differential Diagnosis: When a tall R wave

and a positive T wave are registered in V_1, it is sometimes difficult to differentiate a dorsal infarct from right ventricular hypertrophy. From the electrocardiographic point of view, some diagnostic points should be considered. Thus, in adults positive T waves are exceptional in the right precordial leads in cases of right ventricular hypertrophy. The diagnosis of infarction is further facilitated by the frequent extension of necrosis and/or ischemia to the adjacent areas. The vectorcardiogram in most of these cases is of great help in the differential diagnosis. In cases of dorsal infarction the rotation of the QRS loop in the horizontal plane is predominantly *counterclockwise*, its initial portions are of great magnitude and the speed of inscription is usually increased. In the majority of cases the TsÊ shows the same orientation as the initial portions of the QRSsÊ, being, therefore, directed chiefly forward. In right ventricular hypertrophy, the rotation of the QRSsÊ is predominantly *clockwise* in the horizontal plane, its initial portions usually are not of great magnitude and the speed of inscription is normal or low. The TsÊ has a tendency to oppose the QRSsÊ, being, therefore, directed backward.

In some cases of dorsal infarction in which the QRSsÊ shows a figure-of-eight configuration in the horizontal plane, the vectorcardiographic differential diagnosis of right ventricular hypertrophy may become very difficult. However, the diagnosis of infarction may be suggested by the clinical history, the great magnitude of the initial portions of the QRS loop and the forward orientation of the TsÊ.

Ventricular Activation in Dorsal Infarction: Analysis of vectorcardiograms obtained from patients with dorsal infarcts of the heart shows evidence of modifications in the ventricular activation and repolarization processes. The dead zone, being electrically inactive, does not contribute the vectors which would represent in time and space its activation under normal circumstances. As the result of the necrosis of the dorsal region there is a clear predominance of forward-directed forces corresponding to the portions which are activated early during the ventricular depolarization process. These forces, being oriented forward and to the right, represent early activation of the left septal mass as well as activation of the adjacent myocardial masses of both ventricles, thus permitting the inscription of tall R waves in the right precordial leads.

The aforementioned facts demonstrate that there is a modification of ventricular activation from the very beginning of the process, indicating an early participation of the dorsal region in the depolarization process under normal conditions. According to experimental studies in dogs carried out by Sodi-Pallares et al.,[9] although activation of the epicardium of the left ventricle's free posterior wall is late (about 0.045 second), the total time required for activation of the entire left ventricular endocardium ranges from undetectable figures to values of 0.005 to 0.010 second after the beginning of ventricular depolarization. For these reasons, we believe that the depolarization of the myocardial mass (outer third of the wall) following that of the endocardium in the dorsal region of the left ventricle takes place almost simultaneously with the activation of the septum and adjacent areas. These considerations may explain the fact that dorsal infarctions of the heart modify ventricular activation from the very beginning of the process.

Intraventricular Conduction Disturbances in Dorsal Infarction: Necrosis of the myocardium modifies ventricular activation either by an early lack of electrical forces in the affected region or by the late appearance of forces related to conduction disturbances in the infarcted zone (intra-infarction block).[10] In seven of our cases there was an increase in the speed of inscription of the initial portions of the QRSsÊ which were oriented forward and were of greater magnitude. This increase in the speed of inscription can be related to the absence of opposing forces[6] due to the nonactivation of the dorsal region of the heart. On the other hand, in eleven other cases we observed a greater delay in the inscription and a slight deformity of the terminal portion of the QRS loop, indicating a possible intra-infarction block which retards and renders difficult the depolarization and activation of still viable muscular portions situated within the infarcted area.

In five cases, a peculiar delay and deformity of the initial portions of the QRSsÊ was observed which could be related to septal fibrosis due to diffuse coronary sclerosis.[11] We cannot exclude, however, the hypothesis that these modifications are due to conduction disturbances during the normal activation of the septum and the paraseptal regions, together with the abnormal and opposing activation of certain partially preserved areas within the infarcted zone.

Summary

The vectorcardiograms of twenty-five patients with dorsal infarction of the heart were studied. These infarctions were classified into four groups as follows, all of which showed an increase of the R wave in the B (anterior-posterior) component of Grishman's cube system:

1. Strictly dorsal infarction, showing only an increase of the R wave in the B component. In this group were three cases, including one complicated by complete right bundle branch block.
2. Inferodorsal infarction, showing pathologic Q waves in the C (superior-inferior) component. There were five cases in this class.
3. Laterodorsal infarction, showing abnormal Q waves in the A (right-left) component. Eight cases were placed in this class.
4. Inferolaterodorsal infarction, with abnormal Q waves in the A and C components. There were nine cases, including two complicated by complete right bundle branch block, in this group.

The vectorcardiograms of these cases showed increased magnitude and forward orientation of the initial portions (0.02 second) of the ventricular activation loop. These initial portions frequently had a higher speed of inscription due to the absence of opposing forces. The necrotic areas in the dorsal wall which should undergo early depolarization were not activated at the same time; therefore, no electrical forces were produced in those areas.

In dorsal infarction, the rotation of the QRSsÊ in the horizontal plane was predominantly counterclockwise. This, together with the direction of predominant forces forward (average 0.048 second) and the orientation of the TsÊ in the same direction, facilitates the diagnosis of dorsal infarction in those cases in which a tall R wave in the right precordial leads might suggest right ventricular hypertrophy.

In eleven cases a certain delay of inscription and deformity in the morphology of the terminal portions of the QRS loop was observed. This delay was explained by a possible conduction disturbance during late activation of still depolarizable muscular masses in the infarcted area.

Acknowledgment

We wish to thank Drs. Josef Feher and Moris Chansky for their technical help and kindness in sending us four patients who were included in this paper.

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Unusual Experiences with Precordial Continuous Murmurs*

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A RECENT review by Neill and Mounsey[1] emphasized the fact that a variety of lesions may duplicate the auscultatory findings characteristic of patent ductus arteriosus. Aortic septal defects have first been discovered when the surgeon explored further after his failure to locate a patent ductus arteriosus thought to have been present because of "typical findings." Some of the more commonly listed causes of precordial continuous murmurs are: patent ductus arteriosus, bronchial arterial collateral circulation, pulmonary or systemic arteriovenous fistulas, venous hums, coronary arteriovenous fistulas, ruptured sinus of Valsalva, flow through the collaterals and across the stenotic site in patients with coarctation of the aorta, aortic septal defects and peripheral pulmonary artery stenoses.

The purpose of this report is to describe seven cases presenting continuous murmurs seen over an eighteen month period in order to emphasize the relative frequency with which the clinician may be confronted with unusual causes for this physical sign.

CASE REPORTS

CASE 1. A twenty-two year old white woman (Ev. P.) complained of shortness of breath and occasional fainting after exertion since childhood. Despite these complaints she had led a rather active life.

Examination revealed a well developed, well nourished woman. Cuff blood pressure was 124/64 mg. Hg. The second pulmonic sound was palpable and markedly accentuated. At the apex the first sound was loud and diastole was clear. Just medial to the aortic area, as well as in the infraclavicular areas and over the mid-dorsal paravertebral areas, was heard a faint high-pitched murmur starting early in systole, reaching its greatest intensity at the time of the second sound and continuing thereafter through most of diastole. The remainder of the examination was normal.

Laboratory Findings: Hemogram and urine were normal. Electrocardiograms demonstrated right axis deviation and right ventricular hypertrophy. Chest x-ray films and fluoroscopy demonstrated slight enlargement of the right ventricle, prominent pulmonary artery, pulsations of the hilar vessels and decreased peripheral pulmonary vascularity.

Right heart catheterization in this laboratory revealed right ventricular pressure of 105/0 mm. Hg and pulmonary artery pressure of 105/40 mm. Hg, mean of 70 mm. Hg, normal wedge pressure and brachial arterial pressure of 140/90 mm. Hg with a mean of 115 mm. Hg. The data did not suggest a shunt; cardiac output by the Fick method was 3.5 L./minute, yielding a low cardiac index of 2 L./minute/M^2.

Angiocardiography: The presence of the continuous murmur led us to refer the patient to Dr. Eugene Braunwald of the National Heart Institute for additional study. A cardiac catheterization was similar to the previous study. Selective angiocardiograms with injection into the main pulmonary artery revealed the smaller vessels in the periphery of the lung fields to be definitely diminished in caliber. In several areas it appeared as if the middle sized vessels were stenotic and narrowed abruptly. A lung biopsy was performed revealing no abnormalities of the smaller vessels. Thus, it appeared reasonably well established that the patient had multiple stenoses of the pulmonary artery.

Comment: Although the findings at catheterization were consistent with idiopathic pulmonary hypertension, the lifelong history of debility and the atypically located continuous murmur suggested that this diagnosis might be incorrect. The presence of atypically located systolic or continuous murmurs in a patient with otherwise unexplained pulmonary hypertension

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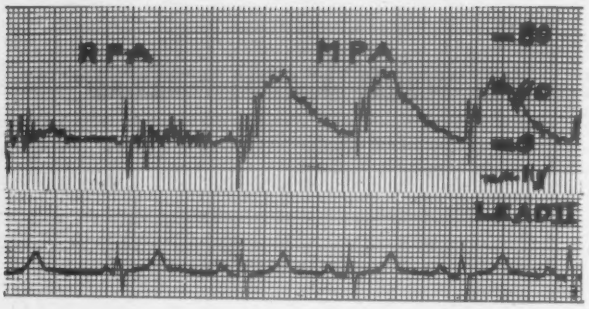

FIG. 1. Case 2. Recording of pull-through from right pulmonary artery (RPA) to main pulmonary artery (MPA) showing abrupt rise in pressure diagnostic of peripheral pulmonary artery stenosis.

should suggest the possibility of single or multiple peripheral pulmonary artery stenosis.[2,3]

In this case, simple catheterization of the pulmonary artery did not demonstrate the lesion(s). The confirmation of a presumed "wedge" pressure by the withdrawal of a blood sample is probably necessary in order to establish the position of the catheter tip in such cases.[3] Selective angiography from the main pulmonary artery or right ventricular outflow tract yields the most complete diagnostic information.[2]

CASE 2. This twenty-two year old white woman (C. B.) had always exhibited cyanosis, shortness of breath on exertion and difficulty in gaining weight. Past history revealed frequent upper respiratory tract infections, but no squatting or overt heart failure. During the past two years she reported having had frequent left chest and arm pains inconstantly related to exertion.

Examination revealed a thin, tall, well developed female who was comfortable at rest. The cuff blood pressure was 100/80 mm. Hg. Cyanosis and moderate clubbing of the fingers and toes were evident. The lungs were clear. The heart was enlarged to the left anterior axillary line and a left parasternal heave was noted. P2 was much louder than A2 and the wide splitting of P2 varied only slightly with respiration. A grade 3, rough, pansystolic murmur was heard over the entire precordium and at the base of the neck. At the base, to the *right* of the sternum, the previously described systolic murmur was noted to extend beyond the second sound through most of diastole as a continuous type murmur with peak intensity at about the time of the second sound. Inside the apex a brief, low pitched, protodiastolic ventricular filling sound was noted.

An electrocardiogram demonstrated right axis deviation and right ventricular hypertrophy. Fluoroscopy revealed pulmonary plethora with intrinsic expansile pulsations of the pulmonary arteries along the right border of the heart. The pulmonary artery

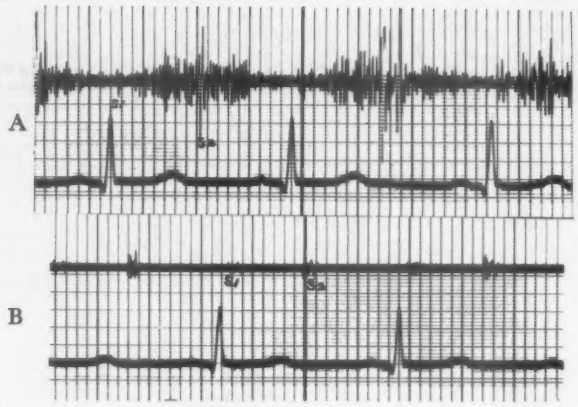

FIG. 2. Case 3. Phonocardiograms demonstrating spontaneous disappearance of the typical ductus murmur. A, pulmonic area. Murmur present, March 25, 1959. B, pulmonic area. Murmur absent, March 25, 1959.

was prominent and the right ventricle considerably enlarged.

Cardiac Catheterization: The results of right heart catheterization in this laboratory were consistent with total anomalous pulmonary venous drainage, atrial septal defect and peripheral pulmonary artery stenosis at or just proximal to the bifurcation of the main pulmonary artery. The latter condition was proved by numerous pull-throughs at the position noted with an abrupt transition from an undulating poorly formed right pulmonary artery pressure contour of 11/5 mm. Hg, mean 7 mm. Hg, to a main pulmonary artery pressure of 52/4 mm. Hg, mean 22 mm. Hg (Fig. 1). A blood sample taken beyond the stenotic site was desaturated to the same degree as the proximal main pulmonary artery sample, indicating that the catheter was not in the wedge position.

Comment: The presence of peripheral pulmonary artery stenosis in an instance of cyanotic congenital heart disease such as this would be expected partially to protect the pulmonary arterioles and veins from the consequences of a prolonged, large increase in pulmonary blood flow. The obstruction(s) probably increased the amount of right to left shunt flow, and added to the burden on the right ventricle. As in Case 1, the major specific clinical finding produced by this complicating condition was the atypically located continuous murmur reminiscent of that heard in cases of patent ductus. The association of this lesion with other congenital cardiac defects is common.[2,3]

CASE 3. The details of this case are reported elsewhere.[4] This nine year old white girl (M. T.) appeared to have a typical patent ductus arteriosus, without pulmonary hypertension, and the clinical impression was proved by cardiac catheterization in

this laboratory. A loud continuous murmur and associated thrill were located in the pulmonic area, but the systolic portion of the murmur was widely transmitted. During periods of quiet rest the murmur often disappeared completely (Fig. 2). The wide pulse pressures recorded when the murmur was present became narrower, largely because of an increase in diastolic pressure, when the murmur was absent. Attempts at making the murmur disappear with various drugs and oxygen mixtures failed.

Attempts were made to correlate the presence or absence of the ductus murmur with the presence or absence of shunt flow. Physiologic dead space/tidal volume × 100 increased from 23 per cent in the supine position to 30 per cent in the standing position while the murmur was present, and from 22 per cent to 49 per cent while the murmur was absent. These data demonstrated a slight decrease in alveolar perfusion in the upright posture when the murmur was present (shunt present) compared to the expected, relatively large, decrease in alveolar perfusion with the assumption of the upright position when the murmur was absent (shunt flow markedly decreased or absent).

At surgery the ductus described a slight curve in its course between aorta and pulmonary artery, and gentle dorsal traction on the pulmonary artery abolished the thrill. This appeared due to further angulation of the ductus so as to close its lumen. Thus, the cause of the intermittent disappearance of the murmur could be ascribed to intermittent kinking of the ductus itself, proabably due to slight shifts in mediastinal structures and to the resultant variations in shunt flow.

Comment: The establishment of a firm diagnosis in this patient had been delayed because of the vagaries of the murmur. Other instances of intermittency of a typical ductus murmur are probably known to some large pediatric clinics, but adequate description and documentation of this phenomenon have thus far been unavailable. It is, therefore, not possible to estimate the frequency with which this occurs.

CASE 4. Since childhood this thirty-nine year old white woman (E. P.) performed strenuous athletics including team sports and skin diving. She was referred to this hospital because of the recent development of atypical precordial pains and the finding of a continuous murmur in the pulmonic area.

Examination was normal save for a relatively faint, high pitched, grade 2 continuous murmur in the second and third intercostal spaces at the left sternal border. This bruit achieved its peak intensity during diastole (between the second and first heart sounds). It was obliterated during a Valsalva maneuver but became accentuated during the first several cardiac cycles after cessation of the strain. Rotation of the head and unilateral and bilateral jugular venous compression did not affect the murmur.

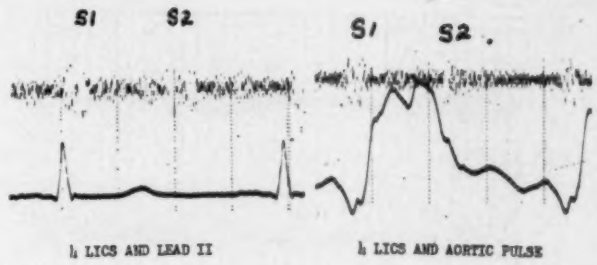

FIG. 3. Case 5. Tracings demonstrating unexplained continuous murmur in the fourth left intercostal space.

Laboratory Findings: Fluoroscopy and multiple x-ray films revealed a mass in the right cardiophrenic angle which appeared to be a lipoma. *Right heart catheterization* in this laboratory revealed normal pressures; no evidence for a right to left or left to right shunt was obtained by blood oxygen analysis and nitrous oxide tests. A venous angiocardiogram was negative for patent ductus arteriosus or pulmonary arteriovenous fistula.

Although the resting electrocardiogram was normal, the electrocardiographic results of a standard exercise test and the presence of elevated serum cholesterol levels suggested that the chest pains were manifestations of ischemic heart disease.

Comment: Despite its "typical" location, the fact that the murmur had its peak intensity during diastole[1] as well as its behavior during and after the Valsalva maneuver indicated that it may have been a venous hum. Despite these characteristics, laboratory studies appeared indicated in order to rule out a patent ductus arteriosus objectively.

CASE 5. This thirty-two year old white woman (L. S.) had congenital maldevelopment of the left wrist and hand, left foot and left eye. She gave no history consistent with debility due to cardiac disease or of the occurrence of rheumatic fever. A heart murmur had been known to be present since the age of eighteen years.

On examination, the blood pressure was 130/70 mm. Hg, pulse 90 and regular. Save for hypoplasia of the areas noted, the patient appeared well. The heart was of normal size and the second aortic sound was slightly louder than the second pulmonic sound. M1 was of good quality at the apex. There was a loud continuous murmur of grade 3 intensity over the entire precordium, loudest in the third and fourth intercostal spaces at the left sternal border (Fig. 3). Electrocardiograms and multiple roentgenograms of the chest were normal.

Catheterization and Angiography: Studies carried out at the National Heart Institute in 1956 included right and left heart catheterization and retrograde

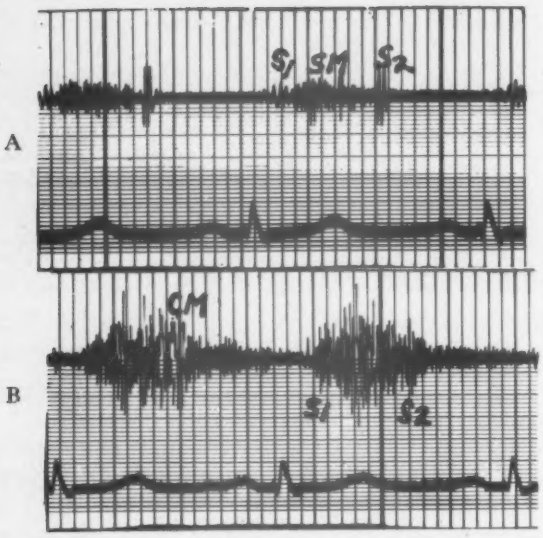

FIG. 4. Case 6. Phonocardiographic tracing demonstrating the production of a continuous murmur (CM) after exercising the left arm. See text for discussion. A, left supraclavicular area at rest. B, left supraclavicular area after exercise of left arm.

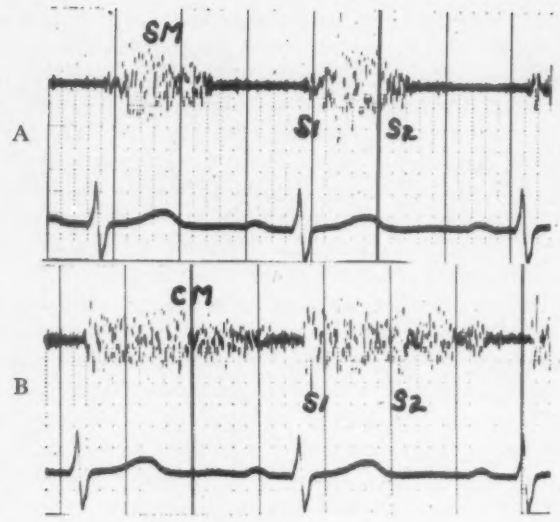

FIG. 5. Case 7. Phonocardiographic tracings recorded at same sensitivity in aortic (A) and pulmonic (B) areas. The diamond-shaped murmur (SM) due to pulmonic stenosis is best appreciated and loudest at the aortic area. The continuous murmur (CM), presumably due to flow in the vessel connecting the systemic and pulmonary circulations, was best heard to the left of the sternum.

thoracic aortograms. They demonstrated a left superior vena cava entering the coronary sinus, prominent aortic insufficiency and an enlarged, somewhat irregular noncoronary sinus of Valsalva.

Comment: Detailed investigation did not explain the continuous murmur. The location of this murmur suggested such possibilities as coronary artery–right ventricular fistula or aortic septal defect which were ruled out by the studies described. Appropriate selective angiography would be required to rule out absolutely a peripheral pulmonary artery stenosis, but this is considered an unlikely possibility in view of the normal right ventricular and pulmonary artery pressures. A continuous murmur, without an explanation for its presence after catheterization, angiography, surgical exploration and postmortem examination, occurred in another patient known to this laboratory.

CASE 6. A fifty-one year old white woman (L. Sc.) was referred for evaluation of a "heart murmur." The patient had experienced acute chest and upper back pain followed by the onset of mild weakness of the left arm some six months before her referral. Serial electrocardiograms taken during this period were all normal. The patient had a past history of cirrhosis of the liver, glomerulonephritis and cystitis.

Physical examination revealed a well developed, slender women. Cuff blood pressure in the right arm was 152/90 mm. Hg, left arm 120/90 mm. Hg and pressures in the legs were 170/100 mm. Hg. Liver palms and scattered spider angiomas were present. The radial and brachial arterial pulsations on the left were definitely diminished as compared with those on the right. The femoral and dorsalis pedis pulses were full and equal bilaterally as were the carotids. In the left supraclavicular area and in the suprasternal notch one could feel a thrill and hear a long stenotic-type murmur occasionally extending for a short period beyond the second sound. The murmur was less loud but easily heard over the base of the heart. Heart size and sounds were otherwise normal. Electrocardiogram, fluoroscopy and multiple roentgenograms of the chest with barium in the esophagus were normal.

Phonocardiographic recordings taken at rest in the left supraclavicular fossa close to the base of the neck revealed a stenotic-type systolic murmur extending through systole and ending just beyond the second heart sound. After raising and lowering the arm thirty times the murmur was noted to extend through the second heart sound as a decrescendo diastolic rumble ending just at or immediately before the onset of the first heart sound (Fig. 4).

Comment: There appeared to be no evidence of cardiac disease or of dissecting aneurysm of the aorta. Although a clinically undetected dissecting aneurysm remained as a possible cause for partial obstruction at the origin of the left subclavian artery, it was believed more likely that atherosclerosis was responsible.[5] Results of the phonocardiographic studies indicated that collateral circulation about the site of obstruction was adequate at rest but inade-

quate during and after exercise to fill the distal arterial system well enough to maintain diastolic blood pressure.[6,7] Thus, what is primarily a systolic gradient of pressure across the stenosis at resting flow rates becomes almost continuously present during the increased flow rates of exercise, producing the systolic-diastolic murmur. The poor prognosis for limb viability reported in such situations was not borne out in the benign course of this patient.[7]

The fact that the murmur could be well heard at the base of the heart initially caused confusion as to the origin of the murmur and raised the question of the presence of acquired or congenital heart disease.

CASE 7. This thirty month old white child (S. H.) had cyanosis, clubbing, episodes of heart failure and multiple bouts of pneumonia since early infancy. A previous catheterization, at the age of one year, was consistent with the tetralogy of Fallot.

Examination revealed a well nourished child, small for her age. Cuff blood pressure was 105/75 mm. Hg, pulse 110. Cyanosis and clubbing of fingers and toes were present. The lungs were clear. Cardiomegaly and a left parasternal heave were noted The second sound was single and loudest at the third left intercostal space at the left sternal border. A harsh grade 4 systolic murmur, with a thrill, was best appreciated at the aortic area and was transmitted to the neck. A grade 3 continuous murmur was heard best along the upper left sternal border and was widely transmitted over the anterior and posterior left hemithorax (Fig. 5). The first sound was of good quality and a brief diastolic rumble was audible at and medial to the apex. The remainder of the examination was unremarkable.

Electrocardiograms showed indeterminate axis and combined ventricular hypertrophy. Roentgenograms and fluoroscopy showed cardiomegaly and intrinsic pulsation of the enlarged hilar vessels. The peripheral pulmonary vasculature appeared normal and equal bilaterally although the right hilum was more prominent than the left.

Cardiac catheterization and selective angiography at the U. S. Naval Hospital, Bethesda, Maryland, demonstrated valvular pulmonic stenosis and right to left shunting at the ventricular level. The main pulmonary artery filled only the right lung via an aneurysmally dilated right pulmonary artery. An anomalous vessel arose from the innominate artery and supplied the left lung with blood. This vessel was stenotic near its origin and led into a markedly dilated fusiform left pulmonary artery. The aortic root was slightly dextroposed.

Comment: This patient represented an additional instance of the rare combination of tetralogy of Fallot with atresia of the left pulmonary artery.[8,9] A continuous murmur is uncommon in typical tetralogy of Fallot, and it usually indicates the presence of bronchial arterial collaterals supplying the lung due to pulmonary atresia or an associated patent ductus arteriosus.[10]

The presence of a continuous murmur in tetralogy of Fallot with atresia of the left pulmonary artery depends on whether or not a branch of the aorta (ductus arteriosus) supplies the left lung and, if so, upon the pressure gradient and volume of flow across the connection between high and low pressure systems. In most of the few reported cases a small connecting vessel was present and only a systolic or no murmur due to flow in this vessel was noted,[8] although rarely, continuous murmurs have been described.[9] The vessel in question probably represents a patent left ductus arteriosus.[9] Nadas and associates[8] pointed out that the pulmonary stenosis murmur was best heard over the nonatretic vessel (aortic area in patients without dextrocardia).

From a therapeutic standpoint, complete correction by means of open heart surgery should be safer in these cases than a Blalock-Taussig procedure since the latter requires the presence of two pulmonary arteries for successful accomplishment of the shunt.[8]

COMMENTS

The cases described illustrate that, when a continuous murmur is found, evaluation of the general clinical status and location and timing of maximum intensity of the murmur may aid in differentiating the actual lesion present from patent ductus arteriosus. Continuous murmurs associated with severe pulmonary hypertension (Case 1) or cyanosis (Case 2) are not likely to be due to a ductus arteriosus; for when a ductus is the underlying basis of such signs, "atypical" auscultatory findings are generally present (systolic, diastolic or no murmur). Nevertheless the vessel between the aorta and left lung, which is undoubtedly responsible for the widely heard continuous bruit in Case 7, has been found to represent a ductus arteriosus on embryologic evidence.[9]

That continuous murmurs may be intermittent in an otherwise "typical" patent ductus is illustrated by Case 3. They also may occur only when exercise produces inadequacy of the collateral circulation about a peripheral site of partial obstruction (Case 6). Straining was noted to make an incompletely explained

continuous murmur transiently disappear in Case 4. Occasionally, despite intensive investigation, continuous murmurs may remain unexplained (Cases 4 and 5).

Experiences such as those herein described have become sufficiently common in the course of evaluating patients for cardiac surgery so that many possibilities must now be considered upon finding a precordial continuous murmur. The pressor test described recently for the enhancement or production of continuous murmurs in atypical cases of patent ductus[11] should be helpful in this regard since a small patent ductus may be difficult to confirm in the absence of extremely sensitive shunt detection methods such as the nitrous oxide and Kr^{85} tests.[12]

Summary

Seven unusual experiences with continuous murmurs are recounted. Two patients had peripheral pulmonary artery stenosis, one had patent ductus arteriosus with intermittent disappearance of the murmur, one had an apparent venous hum, one tetralogy of Fallot with left pulmonary artery atresia and an anomalous branch of the innominate artery supplying the left lung, one a partial blockade to the left subclavian artery with a continuous murmur after exercise and one had aortic insufficiency and no adequate explanation for the murmur after extensive diagnostic work-up.

Care in physical examination may often yield important clues leading to accurate diagnosis.

Acknowledgment

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Electrocardiographic Changes in Recurrent Polyserositis ("Periodic Disease")*

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A CLINICAL SYNDROME of unknown etiology characterized by bouts of fever and pain in the abdomen and chest has been described in the past fifteen years under various designations.[1–5] The underlying pathology of this disorder is a recurrent inflammation of the peritoneum and other serous membranes; therefore, we have suggested naming it "recurrent polyserositis."[5] Others have used such names as "benign paroxysmal peritonitis,"[1] "periodic disease,"[2] "familial Mediterranean fever,"[3] and "familial recurrent polyserositis."[4] The disorder frequently occurs in several members of a family and has been described mainly amongst people of Mediterranean stock.

Although the serous membranes are affected primarily, visceral involvement has also been noted in some cases. Amyloidosis with renal failure eventually develops in a small number of patients.[6–8] French authors[9,10] have described polyarteritis nodosa in the course of the disease in a few patients. Enlargement of the spleen and liver, heart murmurs (usually systolic, at the apex and Erb's point),[3,6] changes in the eye grounds[11] and abnormal electroencephalograms[12] have been noted in some patients and indicate involvement of internal organs. This paper was prompted by the observation of transitory electrocardiographic changes during attacks in three patients suffering from recurrent polyserositis.

CLINICAL MATERIAL

Thirty patients with recurrent polyserositis were examined electrocardiographically. The patients were young people aged fifteen to thirty-five years and had suffered from the disease for two to thirty-two years. All of them had typical paroxysms of fever, pain in the abdomen, the chest and sometimes joints, accompanied by leucocytosis and increased erythrocyte sedimentation rate. The attacks usually lasted one to four days and appeared at varying intervals of four days to several months. In the interval between attacks the patients felt well and were able to perform their daily work.

During an attack the temperature usually rose to 38 to 40°C.; the abdomen became tender and rigid; and chest pain of pleural type caused shallow and rapid respiration. Retrosternal pain was experienced during attacks by one patient before he came under our observation. Many of the patients were subjected to laparotomy because of suspected abdominal disease correctable by surgery. The only finding at laparotomy was acute congestion of the peritoneum, frequently associated with exudation of round cells and eosinophils. No bacteria were ever found in cultures of the peritoneal exudate.

Between attacks the physical findings were absent or scanty; when present they consisted mainly of a palpable spleen and colloid-body-like dots in the ocular fundi.

ELECTROCARDIOGRAPHIC OBSERVATIONS

Electrocardiograms were recorded during attacks in twelve patients. Three of these revealed abnormalities which were not present in the intervals between attacks. The remaining nine patients had normal electrocardiograms, four of them also when re-examined between the attacks. Eighteen patients were examined only in the intervals between attacks and all had normal electrocardiograms.

Following are the case reports of the three patients with abnormal electrocardiograms.

CASE REPORTS

CASE 1. D. R., an eighteen year old boy, of a healthy family, started to suffer from attacks of fever,

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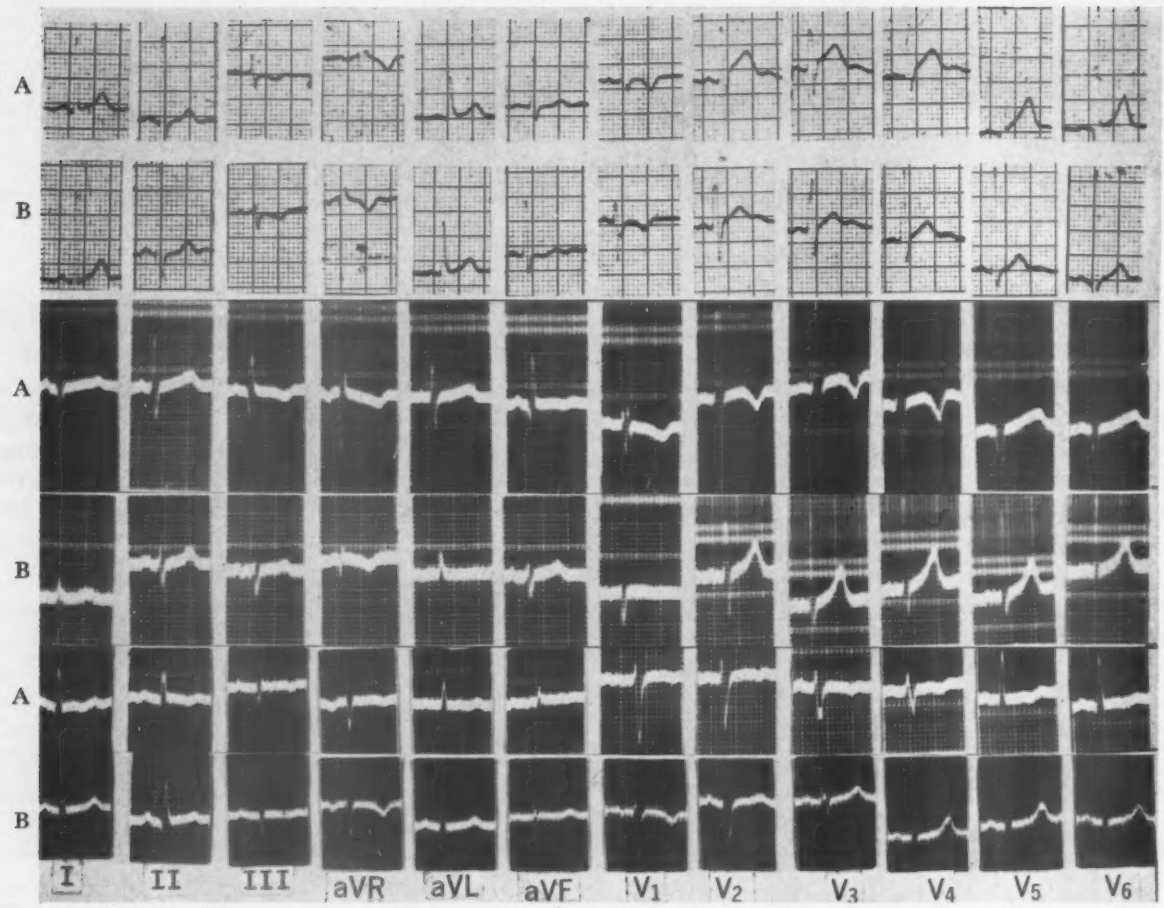

FIG. 1. Electrocardiograms. A, during attack; and B, in the interval between attacks. (Top row, Case 1; middle, Case 2; and bottom, Case 3). Note changes suggestive of pericarditis on day of attack in Cases 1 and 2. Case 3 reveals nonspecific T wave changes during the attack. The electrocardiograms are within normal limits in all cases in the intervals between attacks.

abdominal pain and occasional vomiting at the age of sixteen. The attacks lasted for about twenty-four hours and recurred at intervals of four days to one month. During attacks the leucocyte count would rise as high as 16,000 per cu. mm. and an erythrocyte sedimentation rate of 44/74 mm., first and second hour respectively (method of Westergren), was recorded. Physical examination revealed no abnormalities except for a grade 2, systolic apical murmur suggesting mitral valvular disease. Albuminuria was not present. An x-ray film of the chest revealed slight bulging of the pulmonary conus. Numerous bacteriologic and biochemical examinations were within normal limits.

The electrocardiogram during an attack (Fig. 1A, top) revealed a sinus rhythm of 80 per minute, P-Q interval of 0.14 second, QRS complex 0.08 second, S-T segment slightly elevated in leads I, aVL and more so in V_2-V_6. The T waves were not remarkable. In the interval between attacks the electrocardiogram was within normal limits (Fig. 1B, top).

CASE 2. L. M., a fourteen year old boy, suffered since the age of ten years from attacks of arthritis affecting many of the large joints and accompanied by high fever. Lately, abdominal pain accompanied the attacks which were usually of one to four days' duration and appeared at intervals of one to several weeks. A sister of the patient suffered from a similar disorder and died of amyloidosis. Examination of the patient revealed a grade 2, systolic murmur over the apex and pulmonary valve area as well as a palpable spleen and liver. During an attack the affected joints became warm, swollen and tender and the abdomen distended. The leucocyte count rose to about 11,000 per cu. mm. and the erythrocyte sedimentation rate to 50/85 mm., first and second hour respectively. The urine contained no albumin. The Congo red test was negative. An electroencephalogram performed twelve days after an attack revealed generalized irregularity of background activity, diffuse theta activity and some bursts of slow and sharp waves. Numerous other laboratory examinations were noncontributory.

The electrocardiogram during an attack (Fig. 1A, middle) showed sinus rhythm at the rate of 88 per minute, P-Q interval of 0.16 second, QRS complex of 0.08 second with RR′ peaks in V_1; S-T segment

was isoelectric with a straight ascent to the T waves in leads I, II, V_5 and V_6; in V_2-V_4 the S-T segment was deviated upwards and coved; the T waves were upright but of low voltage in leads I, aVF and peaked and negative in V_2-V_4. Eight days later the electrocardiogram was within normal limits except for low voltage of the QRS complex in the limb leads and shift of the axis to the left (Fig. 1B, middle).

CASE 3. E. L. was a forty-six year old woman. In 1944 the patient began to suffer from attacks of pain in the chest and abdomen accompanied by fever. Pain in the joints and severe headache occasionally accompanied the attacks. The temperature usually rose to 38°C., sometimes preceded by a chill. Each attack lasted one to three days and recurred at irregular intervals of three days to several months. Between attacks the patient felt well and worked as a cook. One of her sons, aged twenty-six, suffered from attacks similar to hers. Physical examination of the patient revealed many white dots diffusely distributed in both eye grounds. The heart and lungs were normal; the liver and spleen were not palpable. During attacks the abdomen became very tender and distended. The white blood count rose to 18,000 per cu. mm. and the sedimentation rate to a maximum of 112/123 mm., first and second hour respectively. On fluoroscopy, limitation of movements of the diaphragmatic leaflets was sometimes observed. Urine analysis was within normal limits. The Congo red test was negative. An electroencephalogram during an attack showed runs of slow activity in the left temporo-occipital region; on another occasion the electroencephalogram was within normal limits. Other laboratory tests were noncontributory.

The electrocardiogram during an attack showed sinus rhythm of 82 per minute, P-Q interval of 0.19 second, QRS complex of 0.07 second, S-T interval isoelectric in all leads; T wave flat, diphasic or inverted in the various leads (Fig. 1A, bottom). Between attacks the electrocardiogram was within normal limits (Fig. 1B, bottom).

COMMENTS

The electrocardiographic changes in these patients affected mainly the S-T segments and the T waves. In one patient (Case 3) they were confined to the T wave and were of nonspecific nature; in the other two patients the changes suggested subepicardial damage. Although definite evidence of a transient inflammatory reaction in the peritoneum and the pleura is available in recurrent polyserositis, no convincing proof of pericardial involvement during the attacks has been offered as yet. Pain of pericardial origin is rarely experienced by these patients. However, it is well known that a transitory inflammatory reaction of the pericardium may pass unaccompanied by pain or any other sign. It is, therefore, conceivable that pericardial involvement as demonstrated by the electrocardiographic changes in Cases 1 and 2 may be more frequent in recurrent polyserositis than hitherto realized.

In some cases of recurrent polyserositis, amyloidosis of the myocardium may develop.[7] As mentioned previously, the sister of the patient in Case 2 died of uremia; autopsy revealed amyloid infiltration of the myocardium, the valve leaflets and the pericardium. The deposition of amyloid is a dynamic process and may possibly explain the electrocardiographic changes during attacks. Furthermore, it has been pointed out by several authors[6,9,10] that a diffuse perivascular inflammatory reaction may occasionally occur in recurrent polyserositis. It is possible that such a reaction is of transitory nature in the early stage of the disease and, if affecting the heart, may cause short-lived changes in the electrocardiogram.

SUMMARY

Thirty patients with recurrent polyserositis were examined electrocardiographically. The electrocardiogram was obtained during an attack in twelve of the patients and in the intervals between attacks in twenty-five patients.

Electrocardiographic abnormalities were noted in only three patients examined during attacks. In two of these patients the changes were suggestive of pericarditis and in one they were not specific and were confined to the T wave. In all three patients the electrocardiograms were within normal limits in the intervals between attacks. In none of the remaining patients examined between attacks were abnormalities present in the electrocardiogram.

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Experimental Studies

Angina Pectoris

V. Giant R and Receding S Wave in Myocardial Ischemia and Certain Nonischemic Conditions*

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INCREASE IN THE amplitude of the R wave and recession of the S wave, together with S-T segment elevation have been clinically observed during severe attacks of the variant form of angina pectoris[1] (Fig. 1A). We have noted similar R, S and S-T changes after acute, severe myocardial infarction. Such R and S wave changes have not been encountered in milder attacks of the variant form of angina pectoris (Fig. 1B) or in milder myocardial infarction.[2]

Hellerstein and Liebow[3] observed that following experimental occlusion of the coronary artery, S-T segment elevation was associated with a delay in the peak of the R wave as well as an increase in its amplitude and a decrease in the amplitude of the S wave. Similar observations were made by Sodi-Pallares,[4] Rakita and co-workers,[5] and Toyoshima and Kutsuna.[6]

This report presents further studies on the significance of the "giant R" wave and receding S wave during ischemia and the results of investigations carried out on R and S wave changes under nonischemic conditions. In addition, data were gathered on reduction in the R wave accompanying marked S-T segment depression as it sometimes occurs in attacks of classic angina pectoris.

METHOD

Forty-two dogs, ranging in weight between 13 and 25 kg., were used in these experiments. Some dogs were used in more than one experimental group. These dogs were anesthetized with pentobarbital sodium, administered intravenously in doses averaging 25 mg. per kg. of body weight. The chest was opened and a large branch of the anterior coronary artery exposed. Tiny recording electrodes measuring 0.1 by 2 mm. were attached to the pericardium at certain points within the area supplied by this artery, selected to include the center or area of greatest ischemia as well as the periphery or area of lesser ischemia. Control electrocardiograms were recorded at this time.

EXPERIMENT 1. R AND S WAVE RESPONSE TO OCCLUSION OF A CORONARY ARTERY

There were thirty separate experiments performed utilizing twenty-three dogs. The exposed branch of the coronary artery was ligated, resulting in a distal area of ischemia. Approximately thirty seconds after ligation S-T segment elevation appeared from the central part of the ischemic area and subsequently from the more peripheral parts. These S-T segment changes have been previously reported in detail[7] and are here referred to only in relation to changes in the R and S waves.

Starting about one and a half minutes after ligation of the artery, the R wave increased in amplitude and the S wave decreased or disappeared completely. These changes were statistically highly significant ($P < 0.003$) three to ten minutes after ligation. Both

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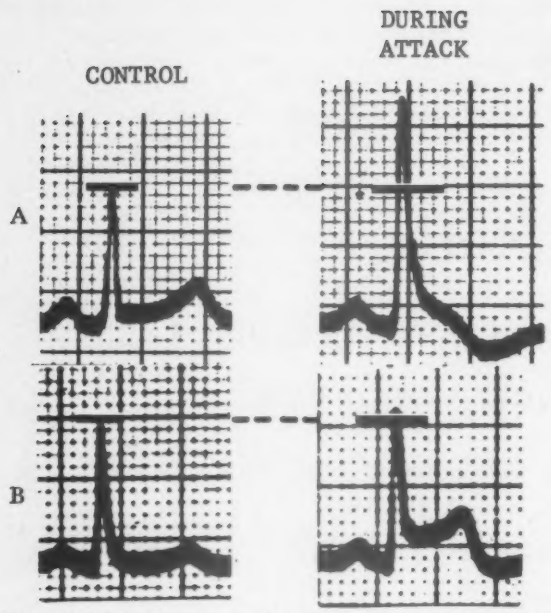


FIG. 1. A, *electrocardiographic changes during a severe attack of the variant form of angina pectoris.* In the control electrocardiogram, before the onset of a severe attack (left), the height of the R wave is 11 mm. During the attack (right) the height of the R wave increased to 18 mm. This change was transient and after the attack the electrocardiogram presented the same appearance as in the control. B, *electrocardiographic changes during a mild attack of the variant form of angina pectoris.* Control electrocardiogram before the attack (left). During the attack (right), no significant change in the height of the R wave occurred. S-T elevation was noted at this time but was transient and disappeared as the attack subsided.

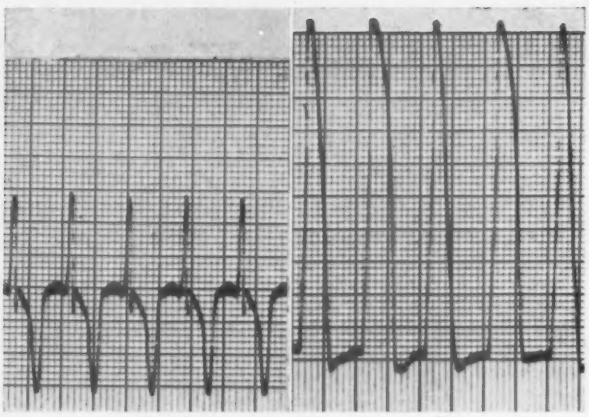


FIG. 3. *Monophasic curve after ligation of a large coronary artery.* A, control electrocardiogram. B, eleven minutes after ligation. Monophasic curve, reaching almost four times the preligation R amplitude, with marked widening of QRS complex. This may be an example of focal block due to local ischemia.

changes occurred earliest and were most pronounced from the center of the ischemic area, the amplitude of the R wave in some experiments reaching twice the control value (Fig. 2, Table 1). In some instances increase of the R wave was preceded by a temporary small decrease which accompanied S-T elevation, the latter occurring after a time lag of about a half minute after ligation of the artery.

Changes in the R and S waves from the

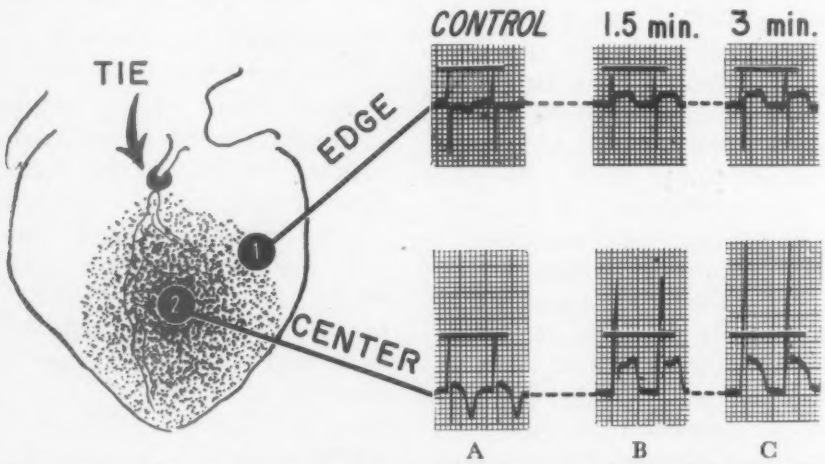


FIG. 2. *R and S wave response to ligation of a large coronary artery.* A, control electrocardiograms were recorded from pericardial electrodes placed at points 1 and 2. The coronary artery then was ligated and a large ischemic area (represented by stippling) resulted. B, one and a half minutes after ligation. From epicardial leads over the center (2) or site of maximum ischemia, the R wave has increased, the S wave is decreased and there is marked S-T segment elevation. From the periphery of the ischemic area (1) the changes in the R wave, S wave and S-T segment are less marked. C, three minutes after ligation. From the center of the ischemic area a giant R wave is now present, the S wave has almost disappeared and there is marked S-T segment elevation. From the periphery no change has occurred in R wave, S wave or S-T segment. Clinically, similar changes can be seen in large acute anterior myocardial infarction.

TABLE I
R, S and S-T Segment Changes (mm.) Following Ligation of a Large Coronary Artery (Experiment 1)

Wave	Control Value	After Ligation (min.)			
		1–2	3	5	10
		A. Central Part of Ischemic Area			
R	15.87 ± 0.97	18.0 ± 1.47	20.62 ± 1.84*	22.88 ± 2.05†	23.29 ± 1.98†
S	10.83 ± 1.01	6.95 ± 1.20*	4.10 ± 1.15†	3.81 ± 1.01†	3.50 ± 1.1†
S-T	1.33 ± 0.34	7.63 ± 0.85†	8.42 ± 1.13†	9.88 ± 1.02†	11.33 ± 1.71†
		B. Intermediate Zone			
R	12.5 ± 1.45	14.4 ± 1.44	...	15.0 ± 1.19*	15.75 ± 1.1*
S	15.0 ± 1.44	14.2 ± 1.86*	...	11.16 ± 1.51*	8.75 ± 0.5†
S-T	2.16 ± 0.38	5.0 ± 0.37†	...	6.67 ± 0.49†	7.75 ± 0.11†
		C. Periphery			
R	10.22 ± 1.38	12.0 ± 1.11	10.84 ± 1.32	13.33 ± 1.61	13.75 ± 1.90
S	15.0 ± 1.86	10.20 ± 2.02	10.50 ± 1.81	10.11 ± 1.93	8.25 ± 2.38*
S-T	0.5 ± 0.16	0.8 ± 0.53	10.33 ± 0.62	2.11 ± 0.57*	2.75 ± 0.28†

NOTE: Values are mean ±S.E.
* Significant difference compared with control value ($P < 0.05$).
† Highly significant difference compared with control value ($P < 0.003$).

TABLE II
R, S, and S-T Segment Changes (mm.) from the Central Part of the Ischemic Area during Ligation and After Release of the Tie on the Coronary Artery (Experiment 2)

Wave	Control Value	After Ligation (min.)		After Release
		5	30	
R	16.73 ± 1.48	20.12 ± 2.32*	24.33 ± 2.52†	17.50 ± 2.08*
S	9.73 ± 0.80	4.94 ± 0.91†	4.50 ± 1.53†	7.63 ± 1.29*
S-T	1.50 ± 0.40	7.75 ± 0.69†	6.67 ± 0.88†	−1.12 ± 0.055†

NOTE: Values are mean ±S.E.
* Significant difference compared with control value ($P < 0.05$).
† Highly significant difference compared with control value ($P < 0.003$).

edge of the ischemic area occurred later and were less marked than changes from the center. The increase in the R wave usually was not as great from the intermediate zone as from the central part and only moderate S-T elevation was encountered from this intermediate area. At the periphery of the ischemic area increase in R and decrease in S wave recordings were usually slight, insignificant or absent; there was only slight S-T elevation or depression.

The amplitude of the R wave increased with time and when it attained about twice the pre-ligation value distinct widening of the R wave often became apparent. This generally occurred five minutes after ligation of the artery. Following widening of the R wave the S wave disappeared and gradually the S-T segment combined with the widened R wave and a monophasic curve resulted (Fig. 3).

EXPERIMENT 2. R AND S RESPONSE TO RELEASING THE TIE ON A LARGE CORONARY ARTERY

In sixteen separate experiments using nine dogs a large branch of the anterior descending coronary artery was ligated, giving rise to a distal area of ischemia. Subsequently, the tie on the coronary artery was released, allowing blood to return to the ischemic area (Table II).

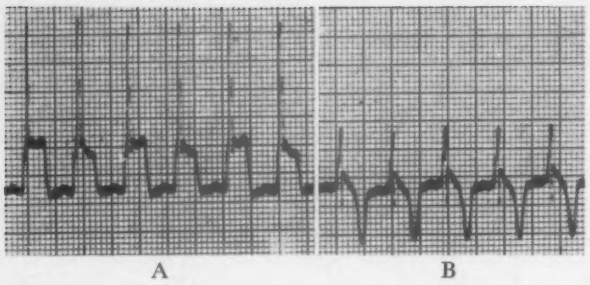


FIG. 4. *R and S wave response to releasing the tie on a large coronary artery.* A, electrocardiogram recorded from the central part of the ischemic area three minutes after ligation of a large coronary artery. Giant R wave, small S wave and marked S-T elevation. B, three minutes after releasing the tie: Marked decrease in the R wave, increase in the S wave and decrease of the S-T elevation.

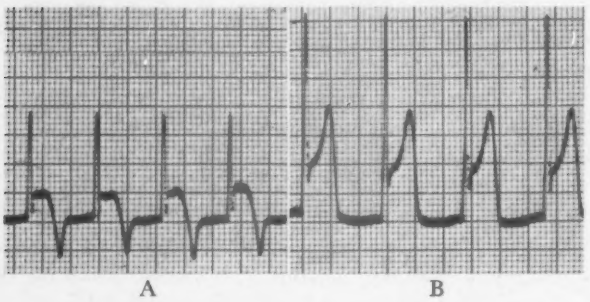


FIG. 5. *R and S wave response to hemorrhagic hypotension in an ischemic area.* A, after ligation of a large coronary artery. Increased R wave and S-T elevation. B, one minute after lowering the mean blood pressure to 40 mm. Hg. Further marked increase in R wave and elevation of S-T segment; S wave diminished. This occurs often but not always.

During the period of ligation, statistically highly significant electrocardiographic changes occurred from the central part of the ischemic area. These changes were increase of the R wave, decrease or disappearance of the S wave and marked S-T elevation.

Following release of the tie on the coronary artery, blood returned to the ischemic area. The R wave immediately decreased in amplitude and gradually returned to the preligation value. The S wave increased in size. (Statistically significant: $P < 0.05$.) The S-T elevation diminished and in some instances transient S-T depression occurred before return to the isoelectric line (Fig. 4).

EXPERIMENT 3. R AND S WAVE CHANGES FROM AN ISCHEMIC AREA; RESPONSES TO HEMORRHAGIC HYPOTENSION AND SUBSEQUENT TRANSFUSION WITH RETURN TO NORMAL PRESSURE

Cardiovascular shock complicating acute coronary occlusion results in decreased coronary flow and further reduction in the blood supply to the ischemic area.[3] In this experiment hypotension was induced following coronary occlusion in order to study the response of the R and S waves.

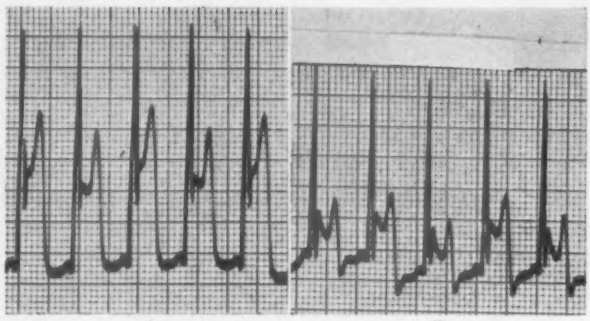


FIG. 6. *R and S wave response in an ischemic area to transfusion following hemorrhagic hypotension.* A, after ligation of a large coronary artery, resulting in hemorrhagic hypotension. Increased R, decreased S, and S-T elevation. B, after transfusion and return of systemic pressure to the approximate prebleeding level. Decreased R, increased S and decreased S-T elevation.

In twenty-five separate experiments using fourteen dogs, a large branch of the anterior descending coronary artery was ligated. This resulted in an increase in the amplitude of the R wave, a decrease of the S wave and S-T segment elevation. About five minutes after ligation of the artery the amplitude of the R wave became relatively stabilized.

Hemorrhagic Hypotension: Hemorrhagic hypotension was produced by reducing the mean femoral pressure to about 40 mm. Hg. After one to two minutes there was usually an additional increase in the R wave as well as a further decrease in the S wave; the S wave occasionally disappeared entirely. Recession of the S wave was paralleled by elevation of the S-T segment (Fig. 5). These changes were most pronounced and statistically highly significant ($P < 0.003$) from the central part of the original ischemic area (Table III), although they appeared to some extent from the intermediate zone and from the periphery.

Transfusion with Return to Normal Pressure: Following a period of hypotension lasting about fifteen minutes, the dogs were tranfused with the blood which had been removed, approximately restoring the mean pressure to the prebleeding level. Immediately after transfusion the R wave usually decreased, the S wave increased and the elevation of the S-T segment decreased significantly ($P < 0.05$) (Fig. 6, Table III).

TABLE III

R, S and S-T Segment Changes (mm.) Following Ligation of a Large Coronary Artery, Following Hemorrhagic Hypotension and Following Transfusion (Experiment 3)

Wave	Control Value	After Ligation (5 min.)	After Hemorrhagic Hypotension	After Transfusion
		A. Central Part of the Ischemic Area		
R	16.41 ± 1.03	23.79 ± 1.85*	28.2 ± 2.13*	25.0 ± 0.86*
S	9.53 ± 1.22	2.57 ± 0.59*	2.0 ± 0.38*	4.83 ± 0.68*
S-T	0.91 ± 0.29	9.29 ± 1.15*	12.0 ± 1.35*	6.67 ± 1.08*
		B. Intermediate Zone		
R	9.89 ± 1.61	11.6 ± 1.62	13.1 ± 1.96	11.4 ± 1.81
S	18.22 ± 1.65	13.8 ± 1.85	13.1 ± 2.04	16.8 ± 2.3
S-T	1.06 ± 0.24	2.50 ± 0.57†	2.8 ± 0.97	−0.7 ± 0.65†

NOTE: Values are mean ±S.E.
* Highly significant difference compared with control value ($P < 0.003$).
† Significant difference compared with control value ($P < 0.05$).

EXPERIMENT 4. R AND S WAVE RESPONSE TO HEMORRHAGIC HYPOTENSION AND SUBSEQUENT TRANSFUSION WITH RETURN TO NORMAL PRESSURE

The purpose of this experiment was to study R wave reduction similar to that which occurs during some severe attacks of classic angina pectoris. In previous experiments[9] islands of S-T segment depression, indistinguishable from that seen in classic angina pectoris, have been produced by hemorrhagic hypotension. The following observations were made in order to investigate the R and S wave changes occurring during such a period of S-T segment depression.

In two experiments, using two dogs, small electrodes measuring 0.1 by 2 mm. were fixed in the pericardium at selected points over the anterior aspect of the heart and control electrocardiograms were recorded (Fig. 7A).

Hemorrhagic Hypotension: Hemorrhagic hypotension was produced by reducing the mean femoral pressure to about 40 mm. Hg. Approximately two minutes later a slight decrease in the R wave amplitude and a slight increase in the S wave was noted but there were no visible S-T segment changes (Fig. 7B). After fifteen minutes, islands of S-T segment depression became clearly defined,[9] and there was a slight additional decrease in R wave amplitude

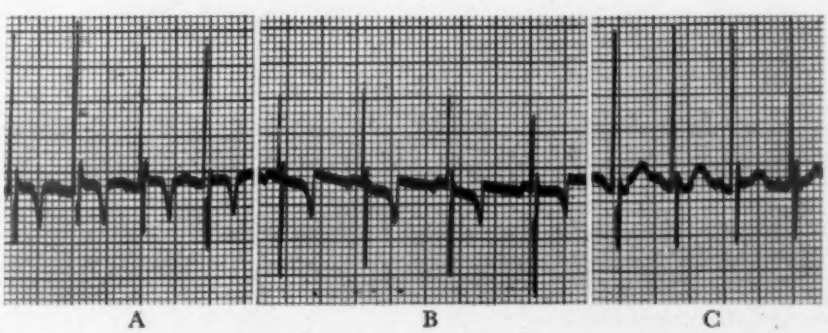


FIG. 7. *R and S wave response to hemorrhagic hypotension followed by transfusion and return to normal pressure.* A, control electrocardiogram. B, fifteen minutes after hemorrhagic hypotension which resulted in decreased R wave and increased S wave. S-T depression appears together with a further decrease in R and an increase in S. C, two minutes after transfusion and return to normal pressure: Marked increase in R, decrease in S and disappearance of S-T segment depression. Records were taken by a fixed electrode, as in all experiments presented in this paper.

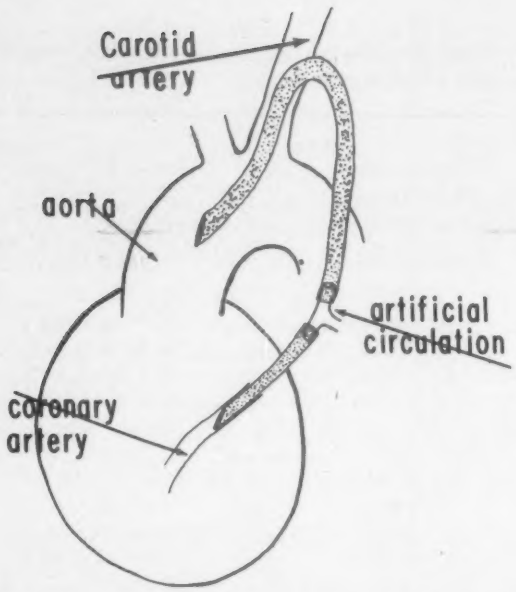


FIG. 8. *Diagram of artificial coronary artery circuit.* A polyvinyl catheter has been inserted through the left carotid artery into the aorta near the ostium of the coronary arteries and is connected with a large branch of an anterior descending coronary artery. A three-way stop cock permits injections. (From: PRINZMETAL, M. et al., *Am. J. Cardiol.*, 3: 282, 1959.[10])

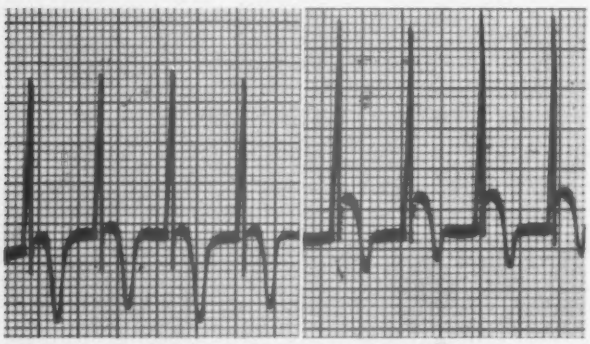


FIG. 9. *R and S wave response to rapid injection of high concentration potassium in saline solution equivalent to normal serum concentration.* A, control electrocardiogram. B, a solution containing 4 mEq./L. of potassium and 142 mEq./L. of sodium was rapidly injected into the coronary circuit. About three seconds later an increase in R, a decrease in S and elevation of S-T appeared.

and a further slight increase in the S wave.

Transfusion with Return to Normal Pressure: Following a thirty minute period of hypotension, the dogs were transfused with the blood which had been removed, restoring the mean pressure to approximately the prebleeding level. The islands of S-T segment depression disappeared and about two minutes after transfusion the R wave increased and the S wave decreased, returning to their control levels (Fig. 7C).

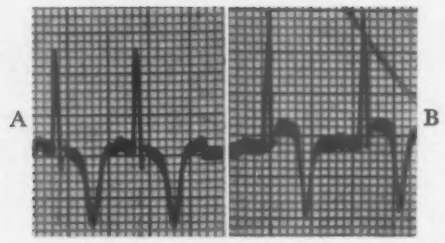


FIG. 10. *R and S wave response to rapid injection of low concentration sodium with potassium.* A, control electrocardiogram. B, a solution containing 103 mEq./L. of sodium with 2 mEq./L. of potassium was rapidly injected into the coronary circuit. About three seconds later an increase in R, a decrease in S and elevation of S-T appeared.

EXPERIMENT 5. RESPONSE OF R AND S WAVES TO CHANGES IN EXTRACELLULAR IONIC CONCENTRATION UNDER NONISCHEMIC CONDITIONS

Characteristic changes in intra- and extracellular electrolytes have been noted previously[10] in ischemia with S-T elevation as well as in ischemia with S-T depression. In ischemia with S-T elevation there is a decrease in the gradient between intra- and extracellular potassium and probably also in the gradient between intra- and extracellular sodium.[10,11] In ischemia with S-T depression the opposite occurs; i.e., there is an increase in the gradient between intra- and extracellular potassium and probably also in the gradient between intra- and extracellular sodium.[10]

Elevation and depression of the S-T segment were also produced in nonischemic conditions by altering the extracellular concentration of these electrolytes. S-T segment elevation was observed after decreasing the intra/extracellular potassium and the extra/intracellular sodium gradients; S-T segment depression was produced by increasing these ionic gradients.[10] The present experiment was undertaken to study the effect of electrolyte changes, that is, alteration of the extracellular concentration of these electrolytes on the R and S waves under nonischemic conditions.

In fifteen experiments using thirteen dogs, a polyvinyl catheter was inserted through the left carotid artery into the aorta near the ostium of the coronary arteries and was connected with a large branch of an anterior descending coronary artery. Injections were made by means of a three-way stopcock connected to the artificial coronary circulation (Fig. 8). Various electrolyte solutions at body temperature in amounts of 5 cc. each were injected rapidly. Electrocardiograms were recorded from small

TABLE IV

R, S and S-T Segment Response (mm.) to Changes in Extracellular Ionic Concentration under Nonischemic Conditions (Experiment 5)

Wave	Before Injection	During Injection	After Injection
	A. Rapid injection of 6 mEq./L. KCl in 142 mEq./L. NaCl		
R	7.02 ± 0.014	10.05 ± 0.21*	7.60 ± 0.065*
S	2.93 ± 0.057	1.99 ± 0.105*	2.85 ± 0.05
S-T	0 ± 0	2.91 ± 0.24*	0 ± 0
	B. Rapid injection of 2 mEq./L. KCl in 103 mEq./L. NaCl		
R	6.27 ± 0.065	9.13 ± 0.08*	8.0 ± 0.098*
S	6.70 ± 0.096	3.90 ± 0.05*	6.0 ± 0.13*
S-T	0 ± 0	1.00 ± 0.07*	0 ± 0
	C. Rapid injection of 171 mEq./L. NaCl		
R	10.45 ± 0.033	9.0 ± 0.13*	10.46 ± 0.027
S	9.03 ± 0.47	10.27 ± 0.14†	8.92 ± 0.10
S-T	0 ± 0	−0.82 ± 0.07*	0 ± 0
	D. Rapid injection of 1 mEq./L. KCl in 142 mEq./L. NaCl		
R	19.6 ± 0.16	18.3 ± 0.16*	19.5 ± 0.084
S	20.25 ± 0.18	20.87 ± 0.25†	19.68 ± 0.13
S-T	0 ± 0	−1.096 ± 0.08*	0 ± 0
	E. Rapid injection of 5 per cent glucose solution		
R	10.38 ± 0.08	26.24 ± 0.16*	10.9 ± 0.08*
S	10.94 ± 0.16	0 ± 0	10.64 ± 0.14
S-T	0 ± 0.0	4.27 ± 0.15	6.84 ± 0.08*

NOTE: Values are mean ±S.E. In all five experiments R wave, S wave and S-T segment response showed a highly significant difference between values during and after injection ($P < 0.003$).

* Highly significant difference compared with control value ($P < 0.003$).

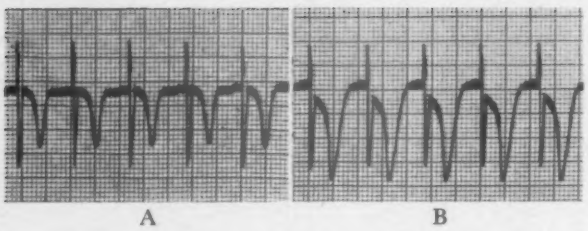
† Significant difference compared with control value ($P < 0.05$).

electrodes attached to the pericardium at selected points over the area supplied by this coronary artery.

High Concentration Potassium with Normal Sodium (Experiment 5A): Solutions containing 4 mEq./L. or more of potassium and 142 mEq./L. of sodium were injected into the coronary artery circuit. It has been previously noted that this caused S-T segment elevation.[10] About three seconds after injection a statistically highly significant ($P < 0.003$) increase in the R wave, a decrease in the S wave and elevation of the S-T segment appeared from the area supplied by this coronary artery (Fig. 9, Table IVA). The increase in R and decrease in S persisted as long as the S-T segment remained elevated. The total change in the R and S waves never exceeded 30 per cent of the preinjection R and S wave amplitudes.

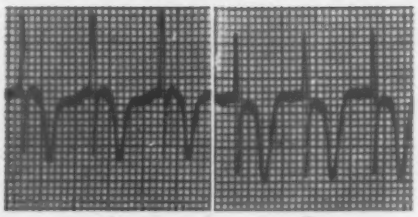
Low Concentration Sodium with Potassium (Experiment 5B): Solutions containing 103 mEq./L. of sodium and 2 mEq./L. of potassium were injected into the coronary artery circuit. These concentrations were above the threshold for hemolysis (0.6 per cent). It has been noted previously[10] that this concentration caused transient elevation of the S-T segment. Almost immediately after injection the R wave increased, the S wave decreased, and slight S-T segment elevation appeared (Fig. 10, Table IVB). The R and S waves gradually returned to their initial amplitudes as the S-T segment returned to the isoelectric line.

High Concentration Sodium without Potassium (Experiment 5C): Solutions containing 155 to 205 mEq./L. of sodium without potassium were



A B

FIG. 11. *R and S wave response to rapid injection of high concentration sodium without potassium.* A, control electrocardiogram. B, a solution containing 171 mEq./L. of sodium was rapidly injected into the coronary circuit. About three seconds later a decrease in R, an increase in S and marked S-T segment depression occurred. Similar changes have been noted in classic angina pectoris.



A B

FIG. 12. *R and S wave response to rapid injection of low concentration potassium in saline solution equivalent to normal serum concentration.* A, control electrocardiogram. B, a solution containing 1 mEq./L. of potassium and 142 mEq./L. of sodium was rapidly injected into the coronary circuit. About three seconds later a decrease in R, an increase in S and S-T segment depression occurred.

injected into the coronary artery circuit. Decrease in R wave, increase in S wave and S-T segment depression occurred almost immediately. The changes became progressively more marked and statistically highly significant ($P < 0.003$) over the next ten to twenty seconds, then gradually returned to preinjection levels (Fig. 11, Table IVC).

Low Concentration Potassium with Normal Sodium (Experiment 5D): Solutions containing 0.5 to 1 mEq./L. of potassium and 142 mEq./L. of sodium were injected into the coronary artery circuit. A statistically highly significant decrease ($P < 0.003$) in the R wave and increase in the S wave appeared almost immediately. S-T segment depression was noted in most animals (Fig. 12, Table IVD).

Five Per Cent Glucose in Water (Experiment 5E): Solutions containing 5 per cent glucose in water were rapidly injected into the coronary artery circuit. A tremendous increase in the R wave (often more than three times the preinjection amplitude) rapidly appeared. Disappearance of the S wave and depression of the S-T segment also occurred almost immediately (Fig. 13, Table IVE). This was the only experimental condition in which an increase in the R wave occurred with S-T segment depression.

COMMENTS

An appreciation of the R and S wave changes occurring in myocardial ischemia is perhaps as important as an understanding of the S-T segment changes which take place. In classic angina pectoris, S-T segment depression is often associated with diminution in the amplitude of the R wave and increase in the S wave. Similar changes have been observed in mild myocardial infarction.[2] In the variant form of angina pectoris, S-T segment elevation is often associated with marked increase in the amplitude of the R wave and diminution of the S wave.[1] Similar changes have been observed in early severe myocardial infarction. All these R, S and S-T changes have been reproduced in animal experiments.

In experiment 1 it was demonstrated that ligation of a large coronary artery resulted in an increase of the R wave, a decrease of the S wave and an elevation of the S-T segment. From the central part of the ischemic area this increase in the R wave was so pronounced (often reaching more than twice the preligation amplitude) that this feature has since been described as a "giant R" wave. R, S and S-T changes were less marked from the intermediate zone and occurred to an even lesser degree from the periphery of the ischemic area. These experimental findings are similar to clinical observations made during acute myocardial infarction.

Upon release of the tie and restoration of blood supply (experiment 2) ischemia became progressively less severe and the large R wave receded, gradually returning to the preligation amplitude. At the same time an increase in the S wave was noted. Similar R and S changes have been observed in patients with the variant form of angina[1,10] (Fig. 14).

Experiments 1 and 3 demonstrated that the appearance of a giant R wave is related to the degree of ischemia, occurring where ischemia is most severe and usually associated with the most pronounced S-T elevation. Increase in the R wave, decrease in the S wave and increase in S-T segment elevation recorded near the periphery of the ischemic area (observed in experiment 3 following hemorrhagic hypotension) are best explained by increased severity of ischemia in this area. Conversely, the de-

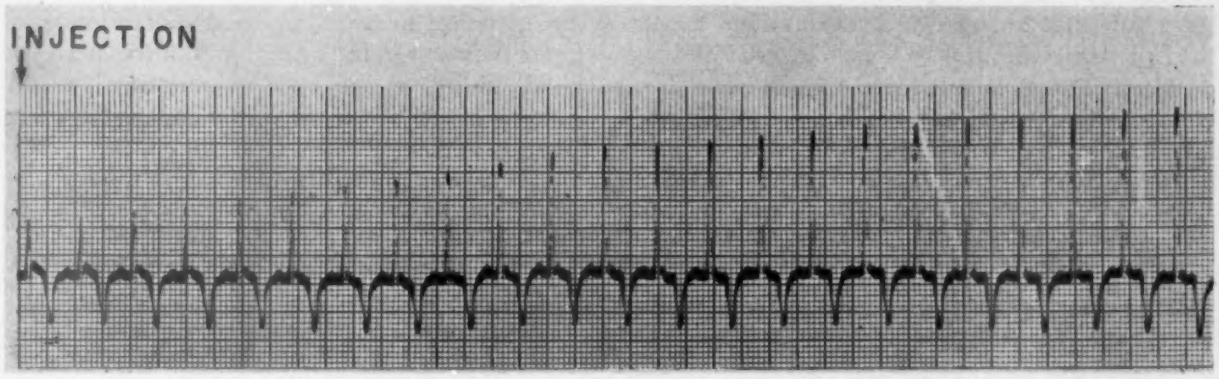


FIG. 13. *R and S wave response to rapid injection of 5 per cent glucose in water.* A solution containing 5 per cent glucose in water was rapidly injected (*arrow*) into the coronary circuit. Almost immediately a tremendous increase in the R wave, disappearance of the S wave and depression of the S-T segment occurred.

crease in the R wave from the periphery of the ischemic area after transfusion, as observed in experiment 3 can be ascribed to decreased severity of ischemia in this area after restoration of normal blood pressure.

This finding emphasizes the importance of recognizing an increased R wave following coronary occlusion. Clinically, a giant R wave may occur in the acute stage of severe coronary occlusion complicated by shock. Experiment 3 demonstrates that shock occurring as a complication of coronary occlusion increases the severity of ischemia and restoring the blood pressure to normal reduces its severity.

In ischemia with S-T segment depression, as produced by hemorrhagic hypotension in experiment 4, the R wave decreased and the S wave increased in amplitude.[12] These changes are similar to those observed in severe classic angina pectoris and are the opposite of that which occurs in the variant form of angina pectoris when myocardial ischemia results in S-T segment elevation, usually associated with an increased R wave and diminished S wave.

Experimental injection of various solutions into an artificial coronary circuit (experiment 5) demonstrated that variations in extracellular cationic concentration produce characteristic changes in the R and S waves *under nonischemic conditions*. Changes in the R and S waves observed in these experiments are similar to those encountered in ischemia with S-T depression and in ischemia with S-T elevation.

CAUSES OF R AND S WAVE CHANGES

Several explanations for changes in the amplitude of the R and S waves are possible as follows: (1) increase in the membrane action potential of the ischemic cells during depolarization; (2) decrease in the electrical conductivity of the extracellular medium; and (3) changes in the propagation process or ventricular activation.

Membrane Action Potential: Changes in the concentration of intra/extracellular ions in the ischemic area are known to occur. In ischemia with S-T elevation the cell membrane loses its ability to maintain the intra/extracellular cationic gradient to some extent.[10,11] Intracellular potassium leaves the cell and probably increases the extracellular potassium concentration, thereby decreasing the potassium ionic gradient across the cell membrane.[13–15] Extracellular sodium probably enters the cell with

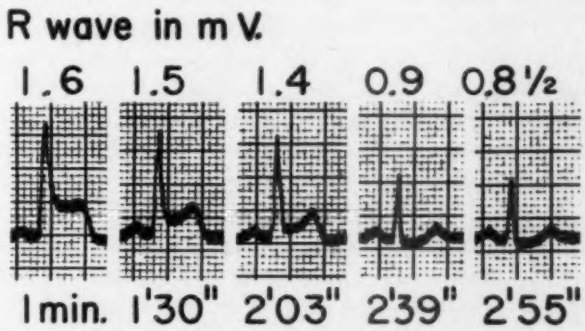


FIG. 14. *R wave changes during and after an attack of the variant form of angina.*[10] A continuous electrocardiogram was recorded. One minute after the onset of pain a large R wave appeared and there was marked elevation of the S-T segment. At one and a half minutes the pain began to subside and disappeared at two minutes. As the pain subsided, both R amplitude and S-T elevation receded. The last electrocardiogram on the right, showing a normal R wave, was recorded slightly less than three minutes after the onset of the attack and one minute after the pain disappeared. The R wave has decreased to about half its magnitude during the height of the attack. R wave and S-T segment elevation increased as ischemia progressed and decreased as ischemia disappeared.

the result that the sodium ionic gradient across the cell membrane also appears to decrease.[11]

When high concentration potassium or low concentration sodium solutions were injected into the coronary circuit, as in experiments 5A and 5B, increase of the R wave, decrease of the S wave and S-T segment elevation appeared despite the absence of myocardial ischemia. In ischemia with S-T depression, there appears to be an increase in the transmembrane cationic gradient.[10] It has been demonstrated that potassium enters the cell, resulting in an increase in the potassium ionic gradient across the cell membrane; at the same time intracellular sodium leaves the cell, probably resulting in an increase in the sodium ionic gradient across the cell membrane. In experiments 5C and 5D, low concentration potassium or high concentration sodium solutions injected into the coronary circuit produced a decrease of the R wave, an increase of the S wave and a depression of the S-T segment.

In all these experiments the onset and duration of R and S wave changes closely paralleled the onset and duration of S-T deviation, whether elevation or depression. Since the transmembrane cationic gradient influences the S-T segment, it would appear that it may also have some effect on the R and S waves and hence on the depolarization phase. The depolarization phase or upswing of the action potential of the cell membrane has been attributed to a sudden influx of sodium ions into the cell due to an increase in membrane permeability.[16] It has been shown by Weidmann[17] that sodium ion permeability is related to the level of the membrane potential (transmembrane cationic gradient) prior to stimulation.

The data from experiment 5 would seem to contradict this explanation. This important point is now being studied by recording intracellular potentials in ischemic and nonischemic conditions.

Electrical Conductivity of the Extracellular Medium: The electrical potential at a given point in the electrical field of the heart is said to vary with the membrane action potential and the conductivity of the extracellular medium. Changes in electrical potential, as already suggested, parallel changes in membrane action potential, but in general are reciprocal to changes in conductivity of the extracellular medium. Thus, if the membrane action potential (ϕ) or solid angle (Ω) increases there is an increase in the electrical potential at a given point. On the other hand, if the electrical conductivity of the extracellular medium (Σ) increases the electrical potential at a given point decreases. This is borne out by basic electrical theory as illustrated in the following equation:

$$E = \frac{\phi \Omega}{4\pi\Sigma}$$

E = electrical potential at a given point
ϕ = electrical moment
Ω = solid angle
Σ = electrical conductivity

In severe ischemia, such as occurs in coronary occlusion, there may be a decrease in the conductivity of the extracellular medium. Accordingly, there should be a reciprocal increase in the electrical potential.

The findings in experiment 5 tend to support this explanation. When a solution with low electrical conductivity, such as 5 per cent glucose in water, was injected into the coronary artery circuit a large change in RS amplitude resulted. Since the R wave amplitude increased and the S wave amplitude decreased, factors other than conductivity were also involved. The injection of glucose, as was shown previously,[10] alters the extracellular ionic concentration and this also affects the membrane action potential. The injection of solutions with high electrical conductivity, such as hypertonic ionic solution, resulted in a decrease in the RS amplitude. These experimental findings support the suggestion that the electrical conductivity of the extracellular medium may influence the RS amplitude. Changes in electrical conductivity of the extracellular medium and other possible factors influencing the RS amplitude are under investigation.

Propagation Process or Ventricular Activation: After ligation of the coronary artery in experiment 1 it was noted that widening of the R wave sometimes took place when its amplitude had significantly increased (Fig. 3). Preliminary observations of intracellular potentials suggest that such a monophasic curve is due to aberration of the propagation process as it passes through the ischemic region. This phenomenon may represent an example of segmental or focal block[18] since the QRS complex in this ischemic area may become very wide.

Summary

1. Increase in the R wave and decrease in the S wave have been clinically observed with myocardial infarction and during episodes of the variant form of angina pectoris.

2. The same changes have been reproduced in experiments with animals by acute ischemia.

3. The electrocardiographic changes were most marked from the center of the ischemic area, where ischemia is most severe, and became progressively smaller as recorded toward the periphery.

4. The term "giant R" wave has been used to describe this marked increase in amplitude of the R wave.

5. The giant R wave has been demonstrated during severe attacks of the variant form of angina pectoris. As pain subsided, the R wave gradually returned to the preattack level. These findings are similar to those observed in experiments on animals after ligation of a large coronary artery and release of the ligation.

6. Hemorrhagic hypotension following coronary occlusion resulted in increased severity of ischemia. There was an additional increase in the R wave and the S wave receded or disappeared. These changes were reversed with return to normal systemic pressure by transfusion.

7. In ischemia with S-T depression due to hemorrhagic hypotension, a decrease in the R wave and an increase in the S wave sometimes occur. This is similar to findings in severe classic angina pectoris. R and S wave changes in ischemia with S-T depression are opposite to those seen in ischemia with S-T elevation.

8. Injection of potassium and sodium in various concentrations directly into a coronary artery produced characteristic R and S changes under nonischemic conditions. High concentration potassium or low concentration sodium resulted in increased amplitude of R waves and decreased amplitude of S waves. Low concentration potassium or high concentration sodium resulted in reduced amplitude of R waves and increased amplitude of S waves. Five per cent glucose in water injected directly into the coronary artery produced a large increase in the amplitude of the R wave and a marked receding or disappearance of the S wave, together with the appearance of S-T depression.

9. Among the explanations for these changes in the R and S waves, the possible role of the membrane action potential, of electrical conductivity of the extracellular medium and of the propagation process have been discussed.

10. Increases in the R wave and decreases in the S wave are noted in severe acute ischemia and may have great clinical significance. When decrease in the R wave and increase in the S wave occur, ischemia probably is less severe in that particular part of the heart.

11. Similar changes in the R and S waves can occur with electrolyte alterations without ischemia.

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Effect of Pentaerythritol Tetranitrate, Amyl Nitrite and Alcohol on Arterial Blood Supply to Ischemic Myocardium*

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VASODILATING drugs have been used for the treatment of coronary heart disease for about ninety years. The literature concerning their mode of action is voluminous and often contradictory. The effects of these drugs on total coronary artery blood flow,[1] contractility and viability of muscle after ligation of a coronary artery,[2] pain,[3] and the electrocardiogram[4] have been investigated.

Direct measurement of blood supply to ischemic muscle as augmented by nitroglycerin was previously reported.[5] This paper concerns the effect of pentaerythritol tetranitrate, amyl nitrite and alcohol on blood supply to ischemic myocardium.

Stenosis or occlusion of a coronary artery produces ischemia in the muscle formerly supplied by the occluded artery. Treatment consists of making blood available to the ischemic area. In the dog heart and in the human heart there is always some blood, in variable amount, that finds its way into ischemic muscle after arterial occlusion. This blood comes from adjacent areas of muscle where the blood supply is normal or almost normal. This blood enters ischemic muscle by way of small arteries that exist in most normal hearts. The beneficial action of a vasodilating drug depends upon the amount of blood delivered through these arterial communications. Direct measurements are valuable if they can be obtained with a fair degree of accuracy.

METHOD OF MEASUREMENT

The amount of blood available to ischemic myocardium can be measured by backflow determinations. The method was described by Anrep and Hausler[6] in 1928 and by Mautz and Gregg[7] in 1937. The method has been used extensively in this laboratory[5] to measure the effect of various surgical procedures on the heart. It consists of ligation of the circumflex branch of the left coronary artery at its origin. This artery is cut distal to the ligature. Arterial blood flows from the cut distal end; this backflow blood is measured and the blood comes from unoccluded coronary arteries by way of intercoronary arterial communications and the flow of blood is in the direction of least resistance. There may be some seepage through the capillary bed. If some blood escapes through the capillaries, it is lost to our measurements. We believe the backflow determinations carried out in a large enough series of experiments have significance. These measurements were made before and after giving the vasodilating drug under test. The difference between the amount of backflow blood before and after is a measure of drug action.

RESULTS

CONTROL EXPERIMENTS

Twelve healthy mongrel dogs were anesthetized with intravenous pentobarbital sodium. The lungs were inflated with oxygen by a Rand-Wolfe respirator. The circumflex branch of the left coronary artery was ligated at its origin and the distal segment was cannulated. A "T" tube was connected to the cannula. Blood from the carotid artery was brought through tubing and "T" tube into the cannula to perfuse the circumflex area of myocardium between backflow determinations. During a backflow determination this perfusion was stopped by clamping the tube from the carotid artery and allowing backflow to occur through the side arm of the "T" tube. Backflow blood was collected for thirty seconds and the result was expressed as cubic centimeters per minute. During the determination the mean aortic blood pressure was kept at 100 mm. Hg. Backflow determinations were made at precise five minute intervals.

Table 1 shows six consecutive backflow de-

* From The Western Reserve University and University Hospitals, Cleveland, Ohio. This work was supported by grants from the U. S. Public Health Service and the Cleveland Area Heart Society.

TABLE I
Control Experiments

Dog No.	Backflow Determinations (cc./min.)				Backflow Determinations (cc./min.)				Difference between Averages
	First	Second	Third	Average	Fourth	Fifth	Sixth	Average	
1	3.6	3.4	3.4	3.5	3.7	3.6	3.6	3.6	0.1
2	4.2	4.8	4.2	4.4	4.4	4.0	4.0	4.1	−0.3
3	13.6	13.0	11.4	12.7	11.8	12.0	11.2	11.7	−1.0
4	6.8	6.8	7.2	6.9	7.2	7.2	6.8	7.1	0.2
5	4.0	3.8	4.0	3.9	4.0	4.0	4.0	4.0	0.1
6	18.0	18.0	18.0	18.0	18.0	18.4	18.8	18.4	0.4
7	3.2	3.4	3.6	3.4	3.6	3.6	3.6	3.6	0.2
8	13.6	10.0	10.4	11.3	10.4	11.2	10.4	10.7	−0.6
9	6.4	6.0	6.0	6.1	6.4	5.6	5.6	5.9	−0.2
10	1.8	1.6	1.4	1.6	1.6	1.9	1.6	1.7	0.1
11	6.8	6.8	6.4	6.7	6.4	6.4	6.4	6.4	−0.3
12	5.2	5.6	5.6	5.5	6.0	5.2	6.0	5.7	0.2
									Mean −0.09

TABLE II
Pentaerythritol Tetranitrate Experiments

Dog No.	Backflow before Drug (cc./min.)				Backflow after Drug (cc./min.)				Difference between Averages
	10 Min. before	5 Min. before	½ Min. before	Average	10 Min. after	15 Min. after	20 Min. after	Average	
13	2.0	2.0	2.0	2.0	2.0	2.2	2.6	2.3	0.3
14	8.2	8.0	8.2	8.1	8.6	9.6	10.4	9.5	1.4
15	6.4	6.0	6.4	6.3	6.8	7.0	7.6	7.1	0.8
16	7.2	7.4	7.2	7.3	8.6	8.6	8.2	8.5	1.2
17	5.2	5.2	5.4	5.3	6.0	6.6	6.8	6.5	1.2
18	2.8	2.6	2.8	2.7	3.2	3.2	3.4	3.3	0.6
19	7.0	6.6	6.6	6.7	6.6	7.2	7.2	7.0	0.3
20	2.2	2.2	2.2	2.2	2.0	2.0	2.0	2.0	−0.2
21	1.2	1.0	1.2	1.1	1.0	1.2	1.4	1.2	0.1
22	7.6	8.2	8.2	8.0	8.8	8.8	8.6	8.7	0.7
23	2.4	2.4	2.4	2.4	2.6	2.6	2.6	2.6	0.2
24	3.0	3.4	3.4	3.3	3.6	3.6	3.6	3.6	0.3
25	2.2	2.2	2.2	2.2	2.0	2.0	2.6	2.2	0.0
26	6.0	5.8	5.6	5.8	5.4	6.0	5.8	5.7	−0.1
27	2.4	2.2	2.6	2.4	2.8	3.0	3.0	2.9	0.5
28	15.6	14.4	14.4	14.8	18.6	19.8	22.2	20.2	5.4
29	4.8	3.6	4.0	4.1	5.8	7.4	5.4	6.2	2.1
30	11.0	10.6	9.4	10.3	9.6	10.0	10.2	9.9	−0.4
31	4.6	4.4	4.6	4.5	5.8	6.2	6.0	6.0	1.5
32	4.8	5.0	4.6	4.8	5.4	5.0	5.2	5.2	0.4
									Mean 0.81

terminations from each of twelve control dogs. The average of the first three determinations was compared to the average of the second three determinations. Statistical analysis of these and subsequent differences was made using a "sum of differences squared" formula. Standard deviation, standard error, "t," and probability (p) were calculated. A probability of five in one hundred ($p = 0.05$) is considered as statistically significant.

The mean difference for control experiments was −0.09 cc. per minute, $t = -0.7730$ and

TABLE III
Amyl Nitrite Experiments

Dog No.	Backflow (cc./min.)		
	5 Min. before Drug	5 Min. after Drug	Difference
33	2.8	3.4	0.6
	2.2	3.2	1.0
	3.2	4.0	0.8
34	5.6	6.2	0.6
	6.6	7.2	0.6
	5.8	6.2	0.4
35	5.6	7.4	1.8
	6.6	7.8	1.2
	6.6	7.0	0.4
	6.6	7.6	1.0
36	6.0	5.6	−0.4
	7.0	8.4	1.4
	8.4	8.4	0.0
37	9.8	11.4	1.6
	8.2	10.0	1.8
	8.0	10.0	2.0
38	3.2	5.8	2.6
	4.2	4.6	0.4
	4.0	4.0	0.0
39	2.0	3.2	1.2
	2.8	3.6	0.8
	2.8	3.6	0.8
40	3.6	5.2	1.6
	4.2	5.6	1.4
	4.8	5.4	0.6
41	7.6	9.0	1.4
			Mean 0.98

$p = 0.45$. The difference is not statistically significant.

PENTAERYTHRITOL TETRANITRATE

Backflow determinations were made in a series of twenty normal dogs. After three successive determinations were found not to vary significantly, 40 mg. of a specially prepared sublingual powder, consisting of one part of pentaerythritol tetranitrate and ten parts of lactose,* was rubbed into the mucous membrane of the dogs' mouths. Backflow determinations were continued at five minute intervals after the drug was given.

Table II shows three backflow determinations obtained before the drug was given and the average of the determinations. The backflow determinations obtained ten, fifteen and twenty minutes after the powder was applied to the mucous membrane and the average are given. The final column shows the difference between the two averages.

In three experiments the backflow after giving the drug was from 0.1 to 0.4 cc. per minute less than the average before giving the drug. In one experiment there was no change. In sixteen experiments the average backflow increased from 0.1 to 5.4 cc. per minute.

The averages were compared and $t = 2.9$ and $p = 0.01$, which is a statistically significant difference.

It was not possible to assess accurately the duration of drug action in these experiments. The maximum effect was observed from twenty- to twenty-five minutes after applying the drug to the mucous membrane.

AMYL NITRITE

The effect of amyl nitrite was measured in nine dogs. Twenty-six determinations were made. After three consecutive backflow determinations showed no significant variation the dog was given amyl nitrite. A perle containing 0.18 cc. of amyl nitrite was crushed inside a 50 cc. syringe. Fifty cc. of air were aspirated into the syringe. This mixture of air and drug was then injected into the lumen of the intratracheal tube. Backflow determinations were made at five minute intervals thereafter. Drug action lasted about ten minutes. After the drug effect subsided, additional doses were given.

The backflow immediately before and five minutes after giving the drug and the difference between the two determinations are shown in Table III. In one experiment the backflow was 0.4 cc. per minute less than the control. In two experiments there was no change from the control, and in twenty-three determinations the backflow increased from 0.4 to 2.6 cc. per minute after the drug was given.

The mean increase was 0.98 cc. per minute. Statistical analysis revealed that $t = 7.2005$ and $p = 0.00004$, which is a statistically significant increase.

ALCOHOL

The effect of alcohol was studied by twelve determinations of backflow in eleven dogs. After control backflow determinations were made alcohol, 500 mg./kg. body weight, was given intravenously. Backflow determinations were made at five minute intervals after giving alcohol. The backflow before and five minutes

* A special sublingual Peritrate® lactose powder was supplied by the Warner Chilcott Laboratories, Morris Plains, New Jersey.

TABLE IV
Alcohol Experiments

Dog No.	Backflow (cc./min.)		
	5 Min. before Drug	5 Min. after Drug	Difference
42	24.0	16.0	−8.0
43	14.0	10.6	−3.4
44	2.6	2.0	−0.6
45	6.6	6.0	−0.6
46	2.4	2.4	0.0
47	2.8	2.2	−0.6
48	2.0	2.0	0.0
49	4.8	4.4	−0.4
50	9.8	5.4	−4.4
51	6.2	2.6	−3.6
52	2.6	2.2	−0.4
	2.4	1.2	−1.2
			Mean −1.93

after giving alcohol and the difference between the determinations are shown in Table IV. In two dogs there was no change after giving alcohol, in ten dogs the backflow decreased from 0.4 to 8.0 cc. per minute.

The mean decrease was 1.93 cc. per minute. Analysis of the differences revealed that $t = 2.7614$ and $p = 0.02$, which is a statistically significant reduction in backflow.

TEST ARTERY LIGATION—MORTALITY, INFARCT SIZE

The effect of pentaerythritol tetranitrate on mortality and infarct size following ligation of a coronary artery was tested in twenty-one dogs.

Twenty-one healthy mongrel dogs weighing from twenty to fifty-four pounds were given oral pentaerythritol tetranitrate,* 20 mg. four times a day for seven days. On the day of operation the dog was given 20 mg. by mouth one hour before operation. After induction of anesthesia 40 mg. of the specially prepared sublingual pentaerythrital tetranitrate lactose powder was rubbed into the oral mucous membrane of the dog. The chest was opened and the anterior descending ramus of the left coronary artery was ligated at its origin. The septal artery was not occluded. After recovery from anesthesia oral pentaerythrital tetranitrate, 20 mg. four times a day, was continued until death or for one week after test artery ligation.

Thirteen of twenty-one dogs died from seventeen minutes to forty-eight hours after the descending coronary artery had been ligated, a mortality of 62 per cent. The eight surviving dogs were sacrificed one month after test artery ligation. The infarct size was observed in seven of the eight hearts. There were five large infarcts, one medium-sized infarct and one small infarct. One heart was inadvertently discarded prior to observation of infarct size.

COMMENTS

In a previous study[5] of the effect of nitroglycerin on the arterial blood supply to ischemic myocardium, it was shown that 0.6 mg. of nitroglycerin increased the backflow from the circumflex coronary artery by an average of 0.88 cc. per minute. It was suggested that this quantity be designated as a nitroglycerin unit. This is the additional quantity of blood brought into ischemic myocardium by way of intercoronary arterial communications as a result of drug action. It is similar, no doubt, to the quantity of blood that produces relief of pain in patients.

The present study has shown that pentaerythritol tetranitrate adds 0.81 cc. of blood per minute or one nitroglycerin unit. Amyl nitrite adds 0.98 cc. or a little more than one nitroglycerin unit. Alcohol, in the dose given, decreased intercoronary flow by 1.93 cc. per minute or by two nitroglycerin units. The clinical response to alcohol is well known. Some patients are relieved of pain, some are not, and in others alcohol seems to aggravate their pain.

Mortality and infarct size following test coronary artery ligation have been studied extensively in this laboratory.[8] The mortality in dogs given pentaerythritol tetranitrate before and after anterior descending coronary artery ligation was 62 per cent and the infarct size in surviving dog hearts was five large, one medium and one small infarct. This mortality and infarct size are about the same as in control animals. This indicates that the addition of one nitroglycerin unit by means of pentaerythritol tetranitrate administration was not sufficient to reduce mortality or prevent muscle destruction following test artery ligation. The artery ligation test is a severe test for one additional cubic centimeter of blood per minute. This addition must be sustained without in-

* Oral Peritrate was supplied by the Warner Chilcott Laboratories, Morris Plains, New Jersey.

terruption for at least forty-eight hours after ligation. Perhaps the drug action was not sustained by the dose schedule used, or perhaps this amount of blood is not sufficient to influence the test. A series of twenty-one dogs is large enough to have some significance.

Summary

1. Treatment of localized myocardial ischemia depends upon addition of arterial blood by way of intercoronary arterial communications.

2. Pentaerythritol tetranitrate adds 0.81 cc. per minute to the ischemic circumflex area of the dog heart.

3. Amyl nitrite adds 0.98 cc. per minute to the ischemic circumflex area of the dog heart.

4. Alcohol decreases intercoronary flow by 1.93 cc. per minute.

5. Increased intercoronary flow resulting from drug action is temporary.

6. Addition of 0.81 cc. per minute as produced by pentaerythritol tetranitrate did not reduce mortality or infarct size following test coronary artery ligation in a series of twenty-one experiments.

Acknowledgment

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Review

Tetralogy of Fallot

Angiocardiographic, Electrocardiographic, Vectorcardiographic and Hemodynamic Studies of the Fallot-type Complex*

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EXTENSIVE CLINICAL EXPERIENCE and investigation by many cardiologists[1–7] during the last seventeen years lead us to extend the old concept of tetralogy of Fallot into the idea of the "Fallot-type complex" which includes any malformation with the clinical picture of tetralogy of Fallot and the same common anatomic denominator, differing only in the functional relationship between the two main morphologic elements of the complex. Of the four elements comprising the tetralogy of Fallot, pulmonary or infundibular stenosis and ventricular septal defect dominate its pathologic physiology; right ventricular hypertrophy is secondary and dextroposition of the aorta is functional rather than anatomic.

As long ago as 1898, Eisenmenger[8] demonstrated that in ventricular septal defect the "pars membranacea" of the septum is anatomically related to the aorta so that the aorta may be dextroposed even though beginning normally in the left ventricle. Selzer[9] noted that the position of the aorta was widely variable in his series of isolated ventricular septal defect. He described some cases in which the aorta arose almost exclusively from the left ventricle in the absence of other associated malformations. He observed a gradual transition from the normal position of the aorta to complete dextroposition.

It is important to know if ventricular septal defect, either isolated or associated with other malformations, has always the same pathogenesis. In Selzer's[10, 11A] series the majority of the septal defects were localized immediately below the aortic valve in the same region as in tetralogy of Fallot and the Eisenmenger complex. Spitzer's[11B] philogenetic and ontogenetic studies on certain cardiac malformations led him to conclude that a single mechanism is responsible for all ventricular septal defects associated with the different types of transposition of the great vessels. In the tetralogy of Fallot, the commonest type of congenital malformation with associated ventricular septal defect, the aorta arises almost exclusively from the left ventricle and the morphologic alterations are practically limited to the stenosis of the right ventricular outflow tract and the associated septal defect. This supports the concept of a common pathogenesis for all subaortic ventricular septal defects.

The various anatomicophysiologic interrelations of the ventricular septal defect and the associated pulmonary and/or infundibular stenosis giving rise to a clinical picture of different severity allow extension of the older concept to the "complex of the Fallot type." Severe valvular pulmonary stenosis (or infundibular stenosis) may present with marked right to left shunt and a clinical picture similar to the tetralogy of Fallot except that the root of the aorta is in its usual position. Kjellberg et al.[6] who include these cases under the heading of "tetralogy of Fallot" point out that clinically "true" truncus arteriosus with aplasia of both branches of the pulmonary artery and supply of

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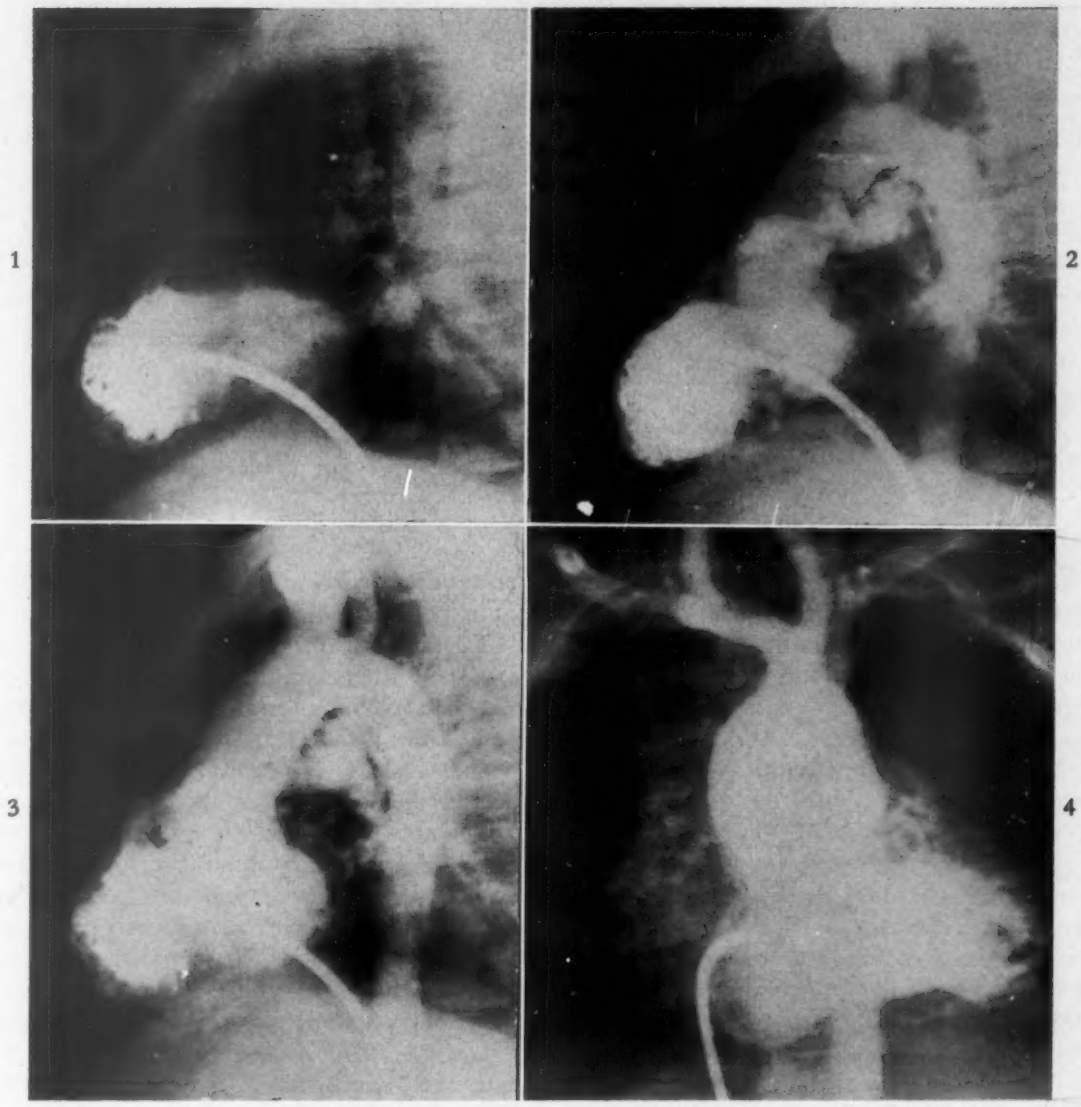


FIG. 1. Case 1, *second angiocardiogram:* The contrast medium injected in the right ve icle passes into the left ventricle through a ventricular septal defect.

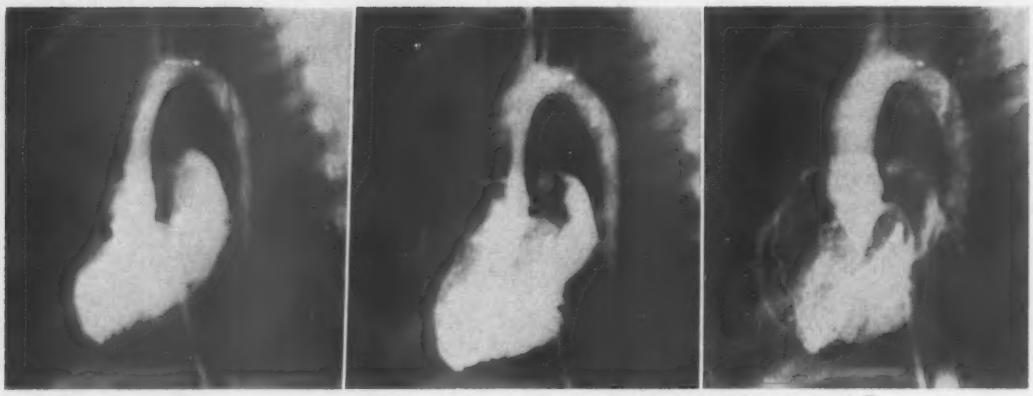
FIG. 2. Case 1, *sixth angiocardiogram:* Both ventricles opacified, aorta overriding the septum.

FIG. 3. Case 1, *tenth angiocardiogram:* Absence of opacification in the infundibular region.

FIG. 4. Case 1, *tenth angiocardiogram:* Posteroanterior plane. Opacification of the aortic branches.

the lungs through the bronchial arteries cannot be distinguished from the tetralogy of Fallot with pulmonary atresia and closed ductus arteriosus (and pulmonary circulation supplied by the bronchial arteries). They include these malformations under the heading of tetralogy of Fallot with pulmonary atresia (the distinction is purely embryologic and anatomic) because the clinical picture is identical. McCord et al.[13] described five types of the tetralogy of Fallot (classic, extreme, slight, predominant ventricular septal defect and predominant pulmonary stenosis) and considered them the clinical and hemodynamic "spectrum" of the association of pulmonary stenosis with ventricular septal defect. These considerations also apply to partial transposition of the great vessels with pulmonary stenosis and ventricular septal defect and to single ventricle with pulmonary stenosis. Both behave clinically like the tetralogy of Fallot.

The complex of the Fallot type, therefore, includes the following six groups: (1) classic tetralogy of Fallot; (2) extreme tetralogy of Fallot (with pulmonary atresia or pseudotruncus arteriosus); (3) so-called acyanotic or slight tetralogy of Fallot; (4) stenosis of the outflow tract of the right ventricle or pulmonary stenosis



5 6 7

FIG. 5. Case 25, *seventh angiocardiogram:* The tip of the catheter is introduced into the right ventricle. Both ventricles are visualized.

FIG. 6. Case 25, *fourteenth angiocardiogram:* Aorta intensely opacified.

FIG. 7. Case 25, *eighteenth angiocardiogram:* Coronary arteries visualized.

with ventricular septal defect and no overriding of the aorta; (5) partial transposition of the great vessels (or transposition of the ventricular chambers) with stenosis of the outflow tract of the right ventricle or pulmonary stenosis and ventricular septal defect; and (6) single ventricle with pulmonary stenosis.

ANGIOCARDIOGRAPHIC DATA

At present, we use selective angiocardiography to clarify the morphologic peculiarities of each case.[14,15] The contrast medium employed is the iodinated compound urographine (a mixture of sodium salts and methylglucaminate of 3,5-diacetyl-amino-2,4,6-triiodobenzoic acid) because it is the least toxic of all iodinated dyes and the general and local tolerance is excellent. In children up to two years of age we injected 1 cc. per kg. of body weight; in patients over two years of age, 1.2 cc. per kg.

In complex of the Fallot type the tip of the catheter is placed in the right ventricle. In one case the catheter passed through the septal defect into the left ventricle where the injection was made. The position was always postero-anterior and lateral. Generally, four exposures per second were made during the first five seconds. Then we allowed a pause of one second in children and two seconds in adults, and proceeded to the second exposure period; two exposures per second were made during the next ten seconds. The pause allowed time for the radiopaque contrast medium to reach the left atrium (beginning of the levogram) without losing pictures and corresponded to the pulmonary circulation time. Although the pressure of the injection depended upon the amount of contrast solution, the injection was made as quickly as possible within one to two seconds.

In this angiocardiographic study of twenty cases, we describe the features of each of the six groups of malformations of the Fallot type as follows:

Group 1, Classic Tetralogy of Fallot: The defect of the interventricular septum is moderate or wide and there is an infundibular and/or valvular pulmonary stenosis of variable severity. An associated interatrial septal defect (pentalogy of Fallot) may exist. The seven patients in this group had marked cyanosis from infancy, intense fatigability and dyspnea on the slightest exertion, clubbed fingers and toes, squatting, grade 2 systolic murmur occupying the first half of systole heard in the third left interspace, "coeur en sabot" on fluoroscopy and polycythemia.

Case 1. Figure 1 (second angiocardiogram) shows that the contrast medium injected into the right ventricle passed into the left ventricle through a ventricular septal defect. In Figure 2 (sixth angiocardiogram) are seen both ventricles, an early opacified, dilated aorta which overrides the septum by about 30 per cent, and a narrowed, irregularly opacified, pulmonary artery. The absence of opacification in the region of the right ventricular outflow tract indicates a marked infundibular stenosis. Figure 3 (tenth angiocardiogram): the contrast medium is homogeneously distributed in the two ventricular chambers. The absence of opacification in the infundibular region is very clear. The ventricular septum and the way both ventricles simultaneously pump the dye into the aorta are perfectly defined. The

FIG. 8. Case 25, *nineteenth angiocardiogram*: Posteroanterior view. Note decrease in pulmonary circulation.

branches of the pulmonary artery are visible. In Figure 4 (tenth angiocardiogram, posteroanterior plane) the structures already described in the transverse plane angiocardiogram are seen as well as the extreme scantiness of the pulmonary circulation and the clear opacification of the aortic branches.

Group 2, Extreme Tetralogy of Fallot with Pulmonary Atresia or Pseudotruncus: Three patients in this group revealed the following clinical symptoms and signs: cyanosis of the face and fingers present from birth; fatigability and dyspnea on exertion; clubbed fingers and toes; polycythemia; grade 1 or 2 precordial systolic murmur, loudest in the third and fourth left interspace, and more intense in the last two-thirds of systole; and accentuation of the second sound. Fluoroscopy revealed "coeur en sabot" with hypertrophy of the right ventricle, normal left atrium and abnormally clear aortic window.

Case 25. In Figure 5 (seventh angiocardiogram) the contrast medium fills the right ventricular chamber and passes through a large septal defect to opacify the left ventricle. A single vessel arising from both ventricles was identified as the aorta. The left atrium was completely opacified during diastole. The catheter, first placed in the right ventricle, passed into the left ventricle where the injection was finished. As noted in Figure 6 (fourteenth angiocardiogram), the two ventricles fill simultaneously with the contrast solution. The aorta is more intensely opacified, the vessels of the arch are more clearly depicted and the emptying left atrium is still visible. Some branches of the coronary arteries may be observed. Figures 7 and 8 (eighteenth and nineteenth angiocardiograms) show a smaller amount of contrast material visualized in both ventricles, the branches of the coronary artery are more clearly defined and the root of the aorta, the vertebral and renal arteries are clearly outlined. In the posteroanterior picture the decrease in pulmonary circulation is remarkable.

Simultaneous opacification of both ventricles when the contrast medium was injected signifies a septal defect which must be large, not only because of the great amount of contrast medium which has passed through it but also because of the admission of the catheter tip into the left ventricle. A single vessel, the aorta, arises from both ventricles. The pulmonary artery and its branches are absent and the pulmonary circulation is very poor, being supplied only by the bronchial arteries. There is no direct or indirect evidence of a patent ductus arteriosus. We think reflux due to mitral incompetence from congenital malformation of the aortic cusp of the mitral valve causes opacification of the left atrium. In our experience this reflux is frequent in cases of large subaortic septal defects. A probe-patent foramen ovale is also possible because the catheter entered the left atrium during the hemodynamic examination. Pseudotruncus, the most severe form of the tetralogy of Fallot, can only be distinguished from "true" truncus by selective angiocardiography but even selective angiocardiography is of no diagnostic help in cases of "true" truncus associated with aplasia of both branches of the pulmonary artery. When pulmonary atresia is accompanied by very slight cyanosis and slight reduction of the functional work capacity patent ductus arteriosus should be suspected.

Group 3, So-called Acyanotic Tetralogy of Fallot or Slight Tetralogy of Fallot: Our series included three cases without cyanosis at rest and two with very faint cyanosis at rest. These patients had no symptoms or signs of respiratory disease or dyspnea but did have slight cyanosis on exertion. There was a systolic thrill in the third left interspace and a loud, grade 3 systolic murmur clearly audible in the third left interspace. There was neither cyanosis nor clubbing of the fingers. On fluoroscopy moderate enlargement of the right ventricle and the pulmonary artery was evident.

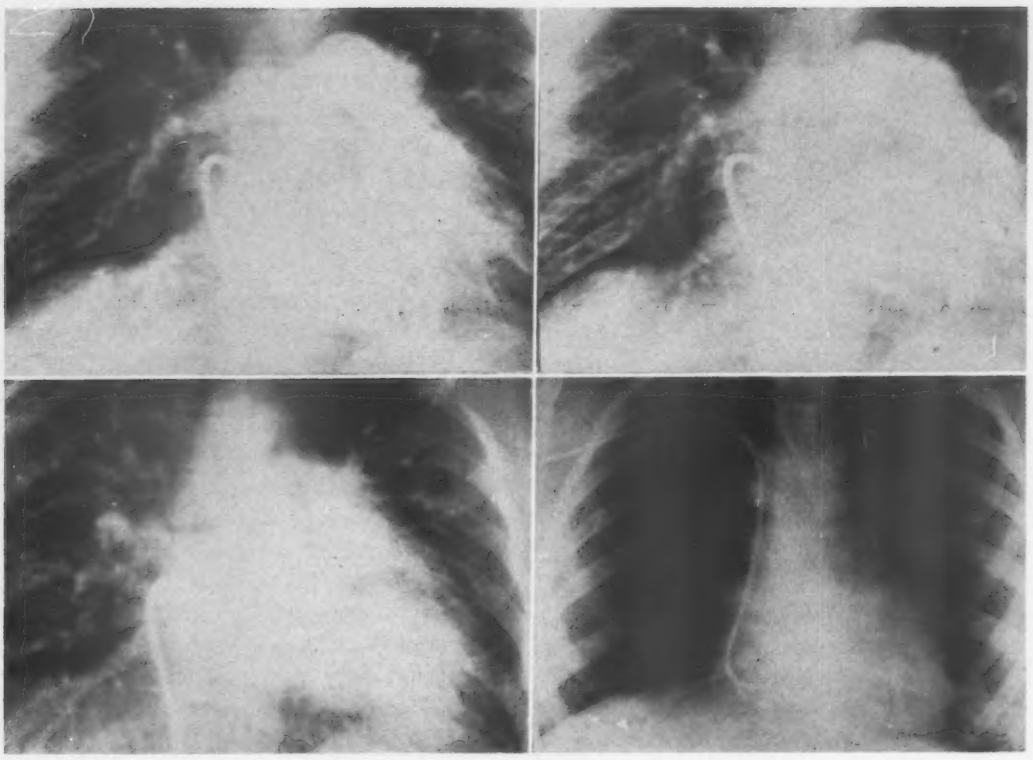


FIG. 9. Case 32, *sixth angiocardiogram:* The opacification of the aorta is faint.

FIG. 10. Case 32, *seventh angiocardiogram:* Aorta visualized above the right branch of the pulmonary artery.

FIG. 11. Case 32, *eighteenth angiocardiogram:* Revisualization of the pulmonary artery.

FIG. 12. Case 32. The catheter entered the aorta during hemodynamic examination.

Case 32. In Figure 9 (sixth angiocardiogram) there is a slight reflux of the contrast solution into the right atrium; the opacification of the aorta is faint and the pulmonary artery is clearly outlined. Figure 10 (seventh angiocardiogram) shows the opacification of the right atrium, left ventricle and pulmonary artery. The aorta may be seen immediately above the right branch of the pulmonary artery. During the levogram (Fig. 11, eighteenth angiocardiogram) there is a more marked opacification of the left atrium, left ventricle, aorta and pulmonary artery. The reopacification of the pulmonary artery suggests the existence of a left to right shunt at the level of the ventricular septum. During hemodynamic examination the cathether entered the aorta (Fig. 12). There is no reduction of the pulmonary circulation. In cases of malformations of the Fallot type presenting with slight cyanosis on exertion the dextrogram may show a faint opacification of the aorta.

Group 4, Stenosis of the Outflow Tract of the Right Ventricle or Pulmonary Stenosis and Large Ventricular Septal Defect without Dextroposition of the Aorta: The two patients in this group present the functional and clinical features of the tetralogy of Fallot without the full morphologic alterations covered by the old concept of the tetralogy of Fallot. They have marked cyanosis, clubbed fingers and a grade 2, precordial systolic murmur, louder in the third and fourth left interspaces. Fluoroscopy shows "coeur en sabot."

Case 37. Figure 13 (fourth angiocardiogram) shows that the dye completely fills the right ventricular chamber and the infundibulum and enters the left ventricle through a septal defect. The clear space between the two ventricles corresponds to the interventricular septum and is visible in this position in cases of right ventricular hypertrophy and clockwise rotation. In Figure 14 (sixth angiocardiogram), opacification of both ventricles and aorta is demonstrated together with a very narrow pulmonary artery whose shadow is superimposed on the image of the catheter at the level of the valvular plane. A small poststenotic dilation precedes the bifurcation of the pulmonary artery. In Figures 15 and 16 (sixth and

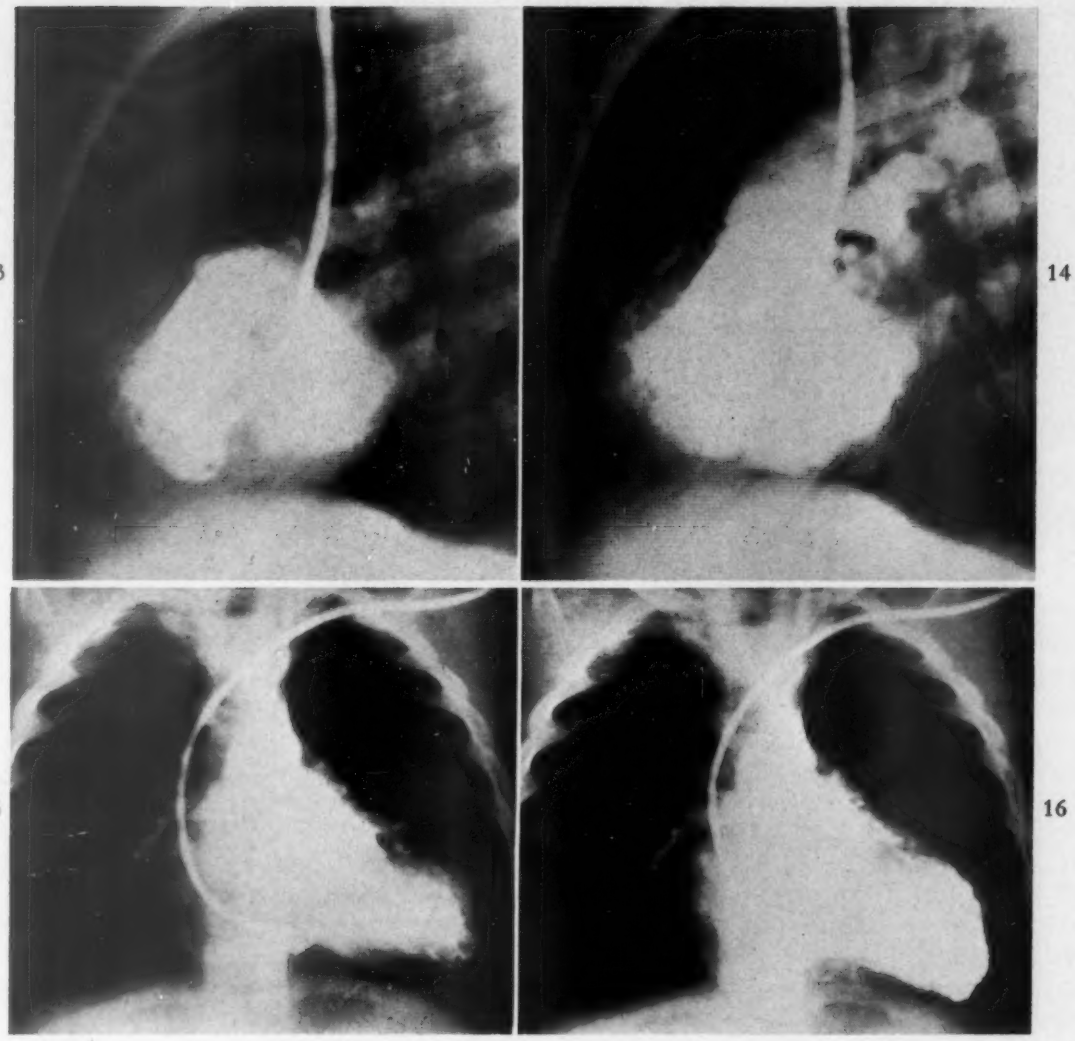


FIG. 13. Case 37, *fourth angiocardiogram:* The contrast medium entered the left ventricle through a septal defect.

FIG. 14. Case 37, *sixth angiocardiogram:* Opacification of both ventricles and aorta; narrow pulmonary artery.

FIG. 15. Case 37, *sixth angiocardiogram:* Posteroanterior view. Visualization of the aorta and pulmonary artery with bifurcation of its right branch.

FIG. 16. Case 37, *seventh angiocardiogram:* Posteroanterior view. Superimposed images of both ventricles; opacification reaching the border of the cardiac shadow.

seventh angiocardiograms) the superimposed images of both ventricles can be seen by the opacification reaching the border of the cardiac shadow. Reflux into the right atrium, the bifurcation of the right branch of the pulmonary artery and the scanty pulmonary circulation are also visible.

Group 5, Partial Transposition of the Great Vessels, Stenosis of the Outflow Tract of the Right Ventricle and Ventricular Septal Defect: Partial transposition accompanied by pulmonary valvular and/or infundibular stenosis behaves functionally like classic tetralogy of Fallot in which a great part of the blood ejected by the ventricles is shunted into the overriding aorta. In the two cases of this group cyanosis was early, severe and accompanied by clubbed fingers and polycythemia.

Case 40. The radiopaque dye fills the ventricular chamber and refluxes into the right atrium in Figure 17 (third angiocardiogram). In Figure 18 (fifth angiocardiogram) the contrast medium fills the right ventricular chamber and visualizes two great vessels; the aorta is the most anterior, the pulmonary artery immediately behind it shows a narrowing

FIG. 17. Case 40, *third angiocardiogram:* Filling of the ventricular chamber and reflux into the right atrium.

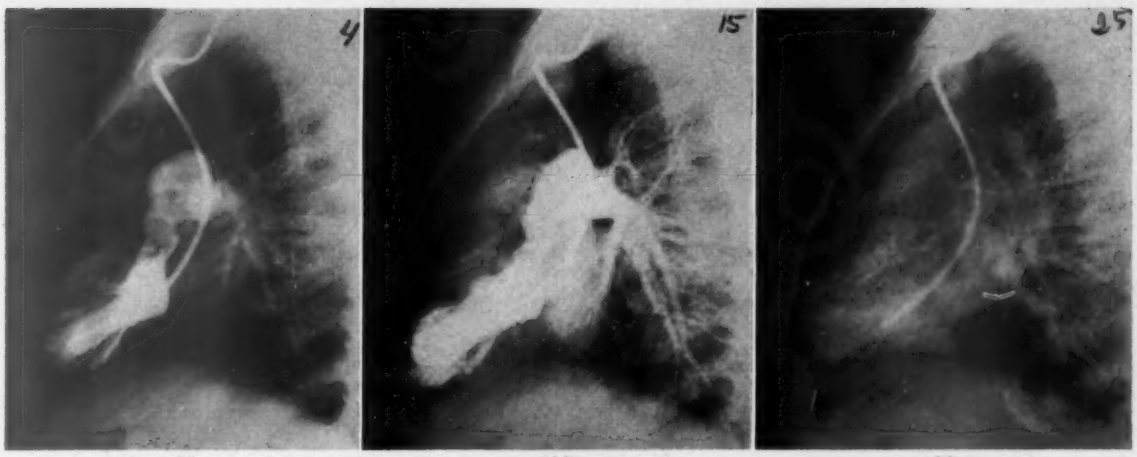
FIG. 18. Case 40, *fifth angiocardiogram:* Visualization of the aorta and pulmonary artery. The pulmonary artery shows a poststenotic dilatation.

FIG. 19. Case 40, *sixth angiocardiogram:* The pulmonary artery arises from the left ventricle and the aorta from the right ventricle.

FIG. 20. Case 40, *sixth angiocardiogram:* Transposition of the great vessels in posteroanterior position.

in its initial portion, probably corresponding to valvular stenosis. Note that the contrast solution opacified the two vessels before completely filling the left ventricle. The pulmonary artery shows a poststenotic dilatation. The heart is in diastole; therefore, the aortic semilunar valves may be clearly seen. As seen in Figure 19 (sixth angiocardiogram), the pulmonary artery clearly arises from the left ventricle but the aorta arising almost completely from the right ventricle seems to override the septum by about 15 per cent. A contrasted shadow corresponding to a small patent ductus arteriosus lies between the pulmonary artery and the aorta and joins them. Figure 20 (sixth angiocardiogram) shows that the aorta and the pulmonary artery assume a peculiar disposition because of the transposition of the great vessels. The ventricular shadows are superimposed. Pulmonary circulation is poor and situs inversus exists. Transposition of the ventricular chambers (or corrected transposition of the great vessels) accompanied by pulmonary valvular and/or infundibular stenosis behaves in the same way. The following angiocardiograms are included in this type.

Case 41. In Figure 21 (fourth angiocardiogram) the catheter outlines the right ventricular



21 22 23

FIG. 21. Case 41, *fourth angiocardiogram:* Poststenotic dilatation of the pulmonary artery.

FIG. 22. Case 41, *fifteenth angiocardiogram:* Aorta larger than normal and placed in front of the pulmonary artery.

FIG. 23. Case 41, *twenty-fifth angiocardiogram:* Return of the contrast medium to the left atrium.

chamber, the infundibulum occupies a posterior position and the pulmonary artery shows a poststenotic dilatation. In the corresponding posteroanterior picture the infundibulum occupies a remarkably central position. The contrast medium faintly outlines the shadow of the aorta; its caliber is larger than normal and in this picture (Fig. 22, fifteenth angiocardiogram) it is placed entirely in front of the pulmonary artery. The corresponding posteroanterior picture depicts the shadow of the aorta with right-sided aortic arch immediately above the clearly defined shadow of the poststenotic dilatation of the pulmonary artery. The levogram (Fig. 23, twenty-fifth angiocardiogram) shows the return of the contrast medium to the left atrium which was also seen in the corresponding posteroanterior picture. Observe the left atrium in systole, the left ventricle in diastole and reopacification of the right ventricle due to a small left to right shunt. In the corresponding posteroanterior picture it is noted that the left ventricle is displaced to the left and its shadow is completely superimposed on that of the spine.

These films demonstrate a ventricular septal defect (opacification of the aorta during the dextrogram) and pulmonary valvular stenosis as shown by poststenotic dilatation. The pulmonary artery is posterior to the aorta. Both pulmonary artery and aorta arise only from the right ventricle and left ventricle, respectively; the ventricular chambers are transposed; pulmonary circulation is sufficient. There is a left to right shunt at ventricular level.

Group 6, Single Ventricle and Pulmonary Stenosis: The patients of this group present cyanosis, clubbed fingers and toes and a grade 2 or 3 systolic murmur in the third left interspace close to the sternum. Fluoroscopy shows an abnormal enlargement of all cardiac chambers. Angiocardiography was performed in one case.

Case 43. Figure 24 (sixth angiocardiogram) shows that the contrast medium fills an abnormally large ventricular chamber, from which two infundibula seem to arise: that of the right ventricle and that of the left ventricle. In the lower border of the opacified chamber in the dextrogram (Fig. 25, tenth angiocardiogram) is a small notch probably corresponding to the origin of the interventricular septum. The roots of the aorta and of the pulmonary artery are more clearly depicted; preceding the latter is a small narrowing which probably corresponds to an infundibular stenosis. It is possible that some dye which returned into the right atrium because of tricuspid incompetence is superimposed on the shadow of the ventricular chamber. The levogram (Fig. 26, twenty-first angiocardiogram) shows marked enlargement of the left atrium and a very dilated left atrial appendage encircling the root of the pulmonary artery. Figure 27 (twenty-sixth angiocardiogram) identifies the single ventricular chamber, left atrium, aorta and pulmonary artery and the infundibular stenosis.

A single ventricle, partial transposition of the great vessels and stenosis of the right outflow tract and possible tricuspid insufficiency are present.

COMMENTS

The angiocardiographic data in this series of

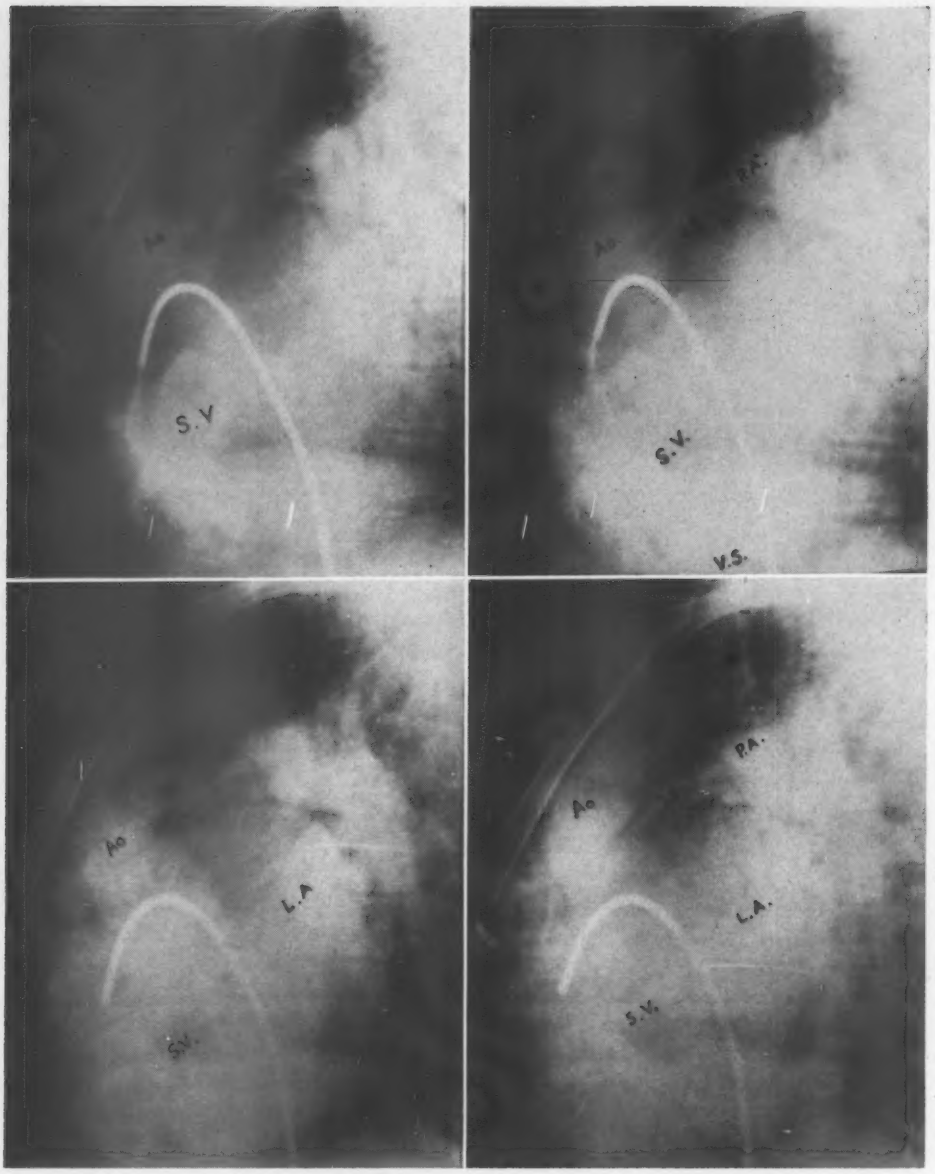


FIG. 24. Case 43, *sixth angiocardiogram:* Large ventricular chamber with two infundibula.
FIG. 25. Case 43, *tenth angiocardiogram:* The roots of the aorta and pulmonary artery clearly depicted.
FIG. 26. Case 43, *twenty-first angiocardiogram:* Marked enlargement of the left atrium.
FIG. 27. Case 43, *twenty-sixth angiocardiogram:* Clear identification of the single ventricular chamber and of the infundibular stenosis.

twenty cases have a number of common features. Right ventricular hypertrophy is revealed by visualization of the thickened trabeculae which bulge into the ventricular chamber and by the extension of the ventricle to the sternocostal plate, especially at the level of the outflow tract. In some cases it was even possible to appreciate the thickness of the ventricular myocardium.

Ventricular septal defect was seen in all angiocardiograms, usually demonstrated directly by passage of the contrast medium from the right to the left ventricle and in other cases indirectly, either by simultaneous opacification of the right ventricle and aorta or by reopacification of the right ventricle during the levogram (especially in patients with only slight cyanosis). Cases of classic and extreme tetralogy of Fallot had no levogram because the greatest part of the contrast material was shunted directly from the right ventricle into the aorta. This phenomenon was produced not only by the stenosis of the right ventricular

TABLE I
Distribution of Stenosis of the Right Ventricular Outflow Tract as Revealed by Angiocardiography (20 Cases)

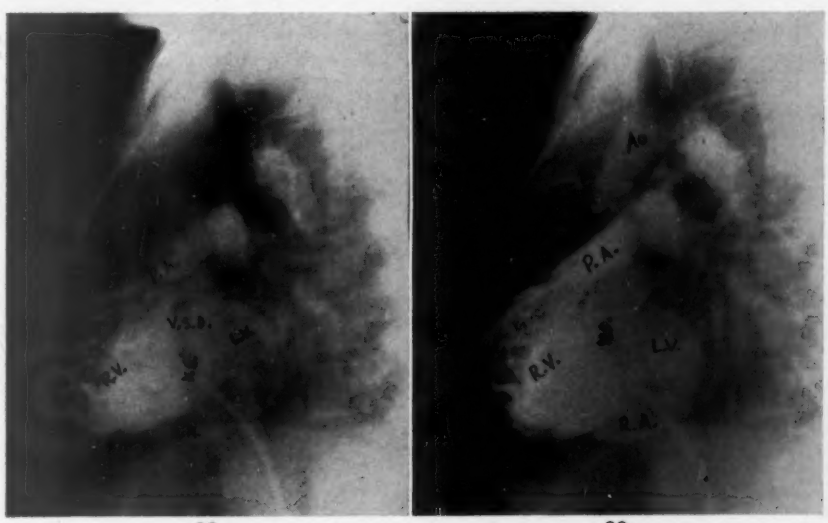
Site	No. of Cases					
	Group 1	Group 2	Group 3	Group 4	Group 5	Group 6
Valvular stenosis	1	...	3	2	2	...
Infundibular stenosis	5	1	2	...	...	1
Infundibular and valvular stenosis	1	...	...	...	...	...
Pulmonary atresia	...	2	...	...	...	...

outflow tract but also by the greater degree of aortic overriding.

Overriding of the aorta was observed except in the presence of slight cyanosis. Visualization of the aorta was then noted only during the levogram and was accompanied by clear re-opacification of the right ventricle. In this way the existence of a left to right shunt at the ventricular level can be demonstrated even when it has not been revealed by the hemodynamic examination. The majority of patients had a right to left shunt (right ventricle to aorta); only one subject had a right to left shunt at the ventricular level accompanying the right ventricle to aorta shunt.

Stenosis of the right ventricular outflow tract, either infundibular or valvular, was always confirmed. Distribution is shown in Table I. In only one case did the hemodynamic examination reveal pulmonary valvular stenosis with greater certainty; angiocardiography alone could not establish or confirm the diagnosis.

Except for three cases, valvular stenosis was more clearly observed in the lateral view and infundibular stenosis was better demonstrated in the posteroanterior position. One patient (Case 8) with aortic valvular stenosis and pulmonary valvular stenosis also had stenosis at the level of the bifurcation and at the beginning of the right branch of the pulmonary artery with agenesis of the upper ramification of this branch (Figs. 28, 29 and 30). The degree of obliquity with which the pulmonary artery crossed with the aorta in lateral views always varied with the degree of dextroposition and overriding of the aorta. The relative position of the two vessels depended on the severity of the malformation (the more horizontal the pulmonary artery, the greater the degree of the aortic overriding, the hypertrophy of the right ventricle and its clockwise



28 29

FIG. 28. Case 8, *sixth angiocardiogram:* Dextrogram showing size of the ventricular septal defect.

FIG. 29. Case 8, *ninth angiocardiogram:* Poststenotic dilatation of the aorta.

FIG. 30. Case 8, *twelfth angiocardiogram:* Posteroanterior view. Abnormal position of the left branch of the pulmonary artery. Right arrow indicates narrowing of right branch of the pulmonary artery, left arrow indicates agenesis of the superior branch of right pulmonary artery.

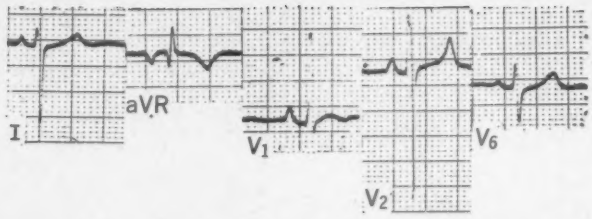


FIG. 34. Group 1. Classic tetralogy of Fallot. Electrocardiogram of a representative case (Case 1). $\hat{A}P$ normally oriented; the P wave is peaked in V_1. Marked right deviation of the mean ventricular electrical axis in the frontal plane, and inclination to the right in the horizontal plane. $\hat{A}T$ directed inferiorly and inclined to the left. Precordial leads show qR pattern in V_6R, V_5R and V_4R; Rs in V_1; and rS from V_2 to V_6 (with abrupt transition from V_1 to V_2). Negative T wave of small amplitude over the right precordium, including V_1.

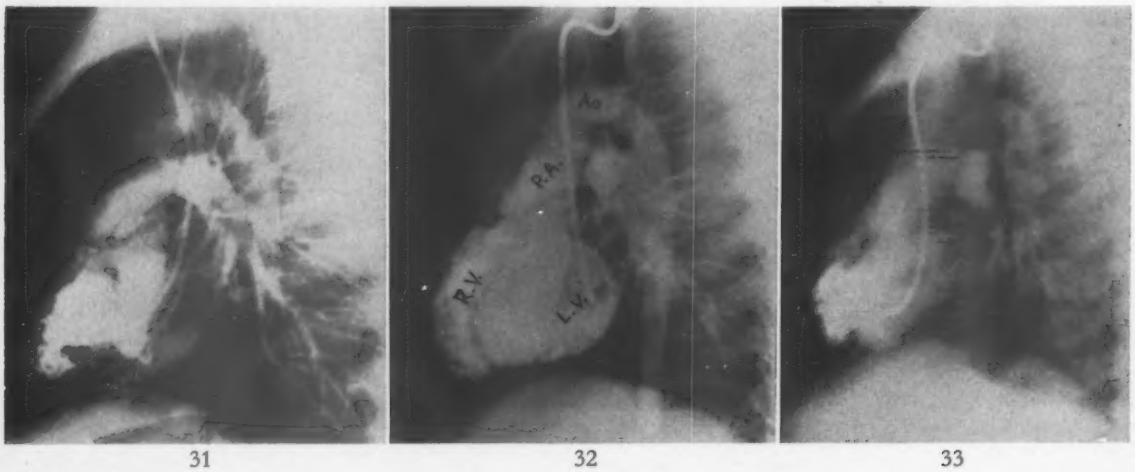
rotation). Angiocardiograms allowed the appreciation of the degree of dextroposition of the aorta in all the cases of complex of the Fallot type. Figures 31, 32 and 33 demonstrate the degrees of dextroposition.

In one of the cases we could verify that there was no inferior vena cava and the catheter introduced through the saphenous vein progressed through the azygos vein into the right atrium. Abnormal venous return was observed in some patients. Angiocardiographic examinations revealed important morphologic details in the malformations of this type and established the basis for a wider concept of the tetralogy of Fallot. They helped to delineate the different anatomic shapes and relative positions of the aorta and pulmonary artery and to distinguish between true transposition and pseudotransposition. Such information unique to angiocardiography provided a better basis for ascertaining the surgical possibilities.

Electrocardiographic and Vectorcardiographic Signs

In this series electrocardiograms consisted of the usual twelve leads and the right precordial leads (V_3R to V_6R). They were always interpreted on a vectoral basis.

The cubic reference frame proposed by Grishman and collaborators was used in all vector-



31 32 33

FIG. 31. Overriding of the aorta of about 20 per cent.
FIG. 32. Overriding of the aorta of about 30 per cent.
FIG. 33. Overriding of the aorta of about 50 per cent.

FIG. 35. Group 1. Classic tetralogy of Fallot. Vectorcardiogram of a representative case (Case 1). The activation (QRS) loop is oriented forward, downward and slightly to the right, being confined to the lower right and anterior octant. It is regularly outlined, without any localized delay of conduction. The initial vectors are directed upward and slightly forward and to the right. The terminal vectors are directed to the right. The loop corresponding to repolarization (T loop), directed downward and to the left, diverges from the QRS loop, the divergence exceeding 90° in the horizontal projection. In the horizontal, sagittal and frontal projections the QRS loop rotates clockwise, counterclockwise and clockwise, respectively.

cardiograms. The plane projections were oriented as if the patient in prone decubitus position was observed from the front (frontal projection), from the right side (sagittal projection) and from above (horizontal projection). In a patient with dextrocardia we changed the spatial orientation of the reference hexahedron accordingly.

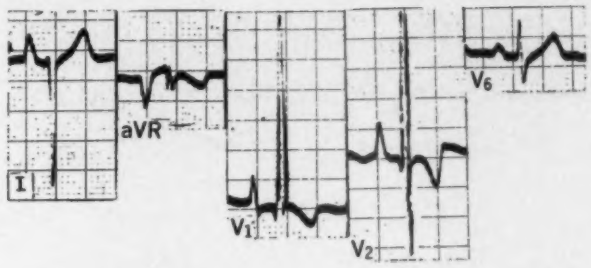


FIG. 36. Group 2. Extreme tetralogy of Fallot. Electrocardiogram of a representative case (Case 25). ÂP normally oriented. Peaked P waves of great amplitude, especially in leads II, aVR, V_1 and V_2. ÂQRS oriented anteriorly, inferiorly and to the right. ÂT directed backward, to the left, and slightly upward. High R waves and negative T waves in leads II and aVF, and persistence of deeply negative T waves until V_4. Small Q waves in V_3R, V_1 and V_2. Very high R waves in V_1, changing sharply to RS pattern in V_2; RS in V_6.

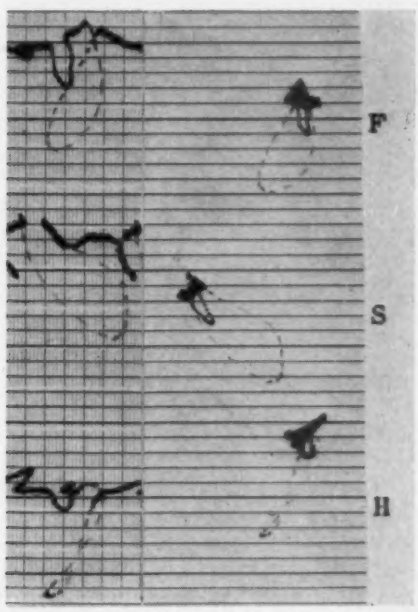


FIG. 37. Group 2. Extreme tetralogy of Fallot. Vectorcardiogram of a representative case (Case 25). The big and elongated P loop is directed downward and anteriorly. The QRS loop is directed predominantly forward and downward and slightly to the right, being confined to the lower right and anterior octant. It is outlined with regularity without localized delays. The initial vectors are directed backward, to the left and slightly upward, while the terminal vectors point forward, downward and to the right. The T loop is divergent from the QRS loop and almost opposed to it in the horizontal projection. The loops rotate clockwise, counterclockwise and clockwise in the horizontal, sagittal and frontal projections, respectively.

ELECTROCARDIOGRAMS

Groups 1 to 3: In the records of the first three groups of Fallot-type complexes, including the

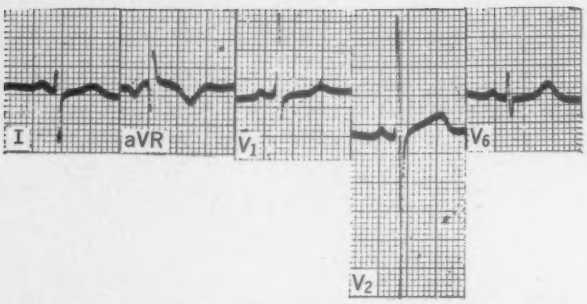


FIG. 38. Group 3. Acyanotic tetralogy of Fallot. Electrocardiogram of a representative case (Case 32). ÂP normally oriented. Normal contour of the P wave in all leads. ÂQRS pointing anteriorly, inferiorly and to the right. ÂT oriented anteriorly, inferiorly and to the left. In aVR the Q wave has the same amplitude as the R deflection. There is no Q wave in the right precordial leads; The Rs pattern in V_3R and V_1 changes to Rs in V_2 through V_1. The T wave is negative in all leads (V_3R to V_7).

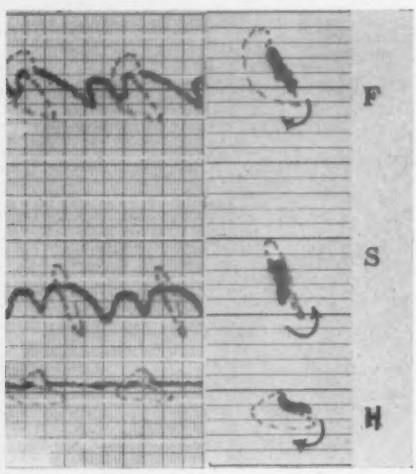


FIG. 39. Group 3. Acyanotic tetralogy of Fallot. Vectorcardiogram of a representative case (Case 32). The P loop is directed downward and to the left as normally. The QRS loop is distributed initially in the lower left and anterior octant and terminally in the upper right and posterior octant. It shows no irregularities or conduction delays. The initial vectors point anteriorly, downward and to the left and the terminal vectors are directed posteriorly, upward and to the right. In the horizontal, sagittal and frontal planes the rotation is clockwise, counterclockwise and clockwise, respectively. The T loop is directed as in the normal, downward and to the left.

acyanotic (Case 32, Fig. 38), classic (Case 1, Fig. 34) and extreme (Case 25, Fig. 36) tetralogy, one can observe a gradual transition of the alterations of the electrocardiogram representing progressive right ventricular preponderance (gradual increase in the amplitude of the R waves in V_1; decrease of the S wave in V_1 until it completely disappears in the extreme case). In these same groups an initial negative

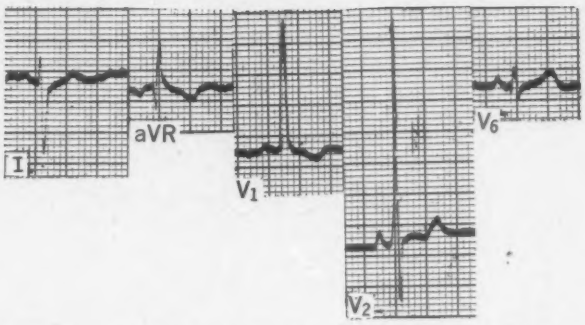


FIG. 40. Group 4. Pulmonic stenosis with ventricular septal defect. Electrocardiogram of a representative case (Case 37). Normal ÂP. P waves of normal shape. ÂQRS oriented anteriorly inferiorly and to the right; ÂT posterior, inferior and left. Besides right axis deviation, the frontal plane leads show no special features. In the right precordial leads there is no Q wave. Gradual transition of the precordial leads with high R wave in V_1 and V_2, Rs in V_3 and V_4, and RS in V_5 and V_6. Negative T wave in V_1.

deflection in V_1 appears; the precordial T waves progressively become negative [T still positive in V_1 (Fig. 38); slightly negative in V_1 and positive in V_2 (Fig. 34); and deeply negative through V_4 (Fig. 36)]. This evolution of the repolarization wave contrasts with the persistence of a sharp transition of the ventricular complexes (Rs to rS) between V_1 and V_2 in all three groups.

The P wave also showed a clear progression, being normal in the acyanotic group; higher and peaked in V_1 in classic tetralogy, and peaked and of high amplitude in leads I, aVR, V_1 and V_2 in the extreme cases.

Group 4: The electrocardiogram of the representative patient in group 4 (Case 37, Fig. 40) is similar to that of cases of isolated pulmonary stenosis, showing a progressive transition of the ventricular complex from V_1 to V_6 with predominant R waves until V_4. The T wave is strongly negative in V_1, predominantly negative in V_2 and positive in V_3. The P waves have no special features.

Group 5: The electrocardiogram of a patient in group 5 (Case 41, Fig. 42), although similar to the records seen in right ventricular preponderance, differs from these in some respects; namely, deep negative deflections in the left precordial leads contrasting with the relatively low amplitude of the R wave on the right side; T wave concordant with the polarity of the main deflection of the QRS complex; very high P waves of increased duration with an independent terminal notch present in all leads and biphid in the left precordial leads,

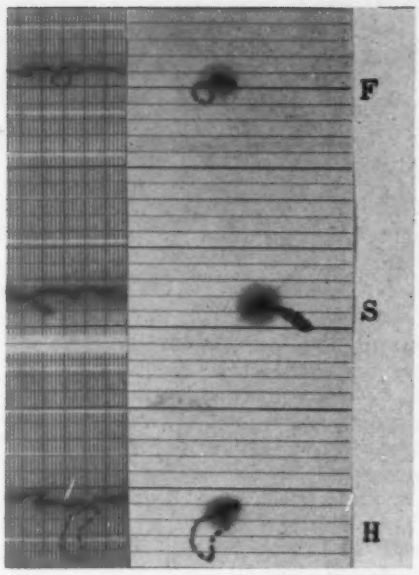


FIG. 41. Group 4. Pulmonic stenosis with ventricular septal defect. Vectorcardiogram of a representative case (Case 37). P loop directed forward and downward with no special features. QRS loop distributed initially in the lower, left and anterior octant and predominantly in the right and anterior octant, with regular speed. The initial portion forms an expansion independent of the main portion of the loop. The main vector points forward and downward. The initial vectors are directed anteriorly and slightly upward; the terminal vectors are oriented anteriorly, inferiorly and to the right. The QRS loop rotates clockwise in the horizontal and frontal projections and counterclockwise in the sagittal projection; in the latter the loop is almost linear. The repolarization loop is spatially divergent, being almost diametrically opposed in the horizontal projection.

suggesting an intraatrial conduction defect.

Group 6: If we did not know the clinical diagnosis and anatomic position of the heart in the patient representing the last group (Case 43, Fig. 44) we would interpret the electrocardiogram as showing left ventricular hypertrophy and strain. However, the cardiac shadow is displaced to the right; therefore, we

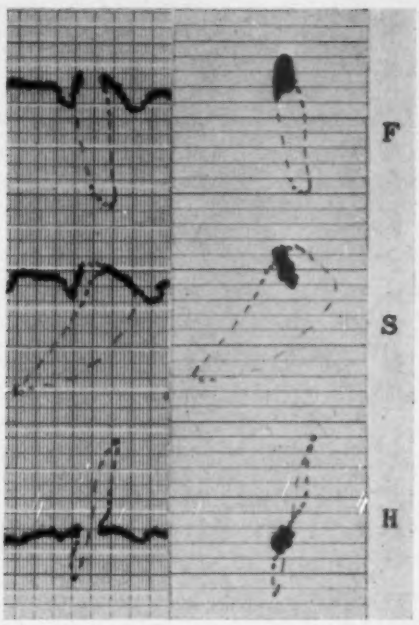


FIG. 43. Group 5. Partial transposition of the great vessels with pulmonic stenosis and ventricular septal defect. Vectorcardiogram of a representative case (Case 41). The P loop is directed straight downward. The main vector of the QRS loop also points almost vertically downward with the loop being displaced first anteriorly and then posteriorly. The plane of the loop coincides with the sagittal plane. There are no irregularities or conduction delays. The sense of rotation is counterclockwise in the frontal plane and clockwise in the sagittal plane. In the horizontal projection the loop adopts a "figure of eight" shape and rotates clockwise in its main (posterior) portion. The initial vectors are small and directed vertically upward. The terminal vectors coincide with the centripetal limb, pointing downward and slightly posteriorly and to the left. The T loop is concordant, being directed vertically downward.

can conclude (considering the normal activation of the atria) that this is not a case of true dextrocardia but rather of dextroposition.

VECTORCARDIOGRAMS

Groups 1 to 3: The vectorcardiograms corre-

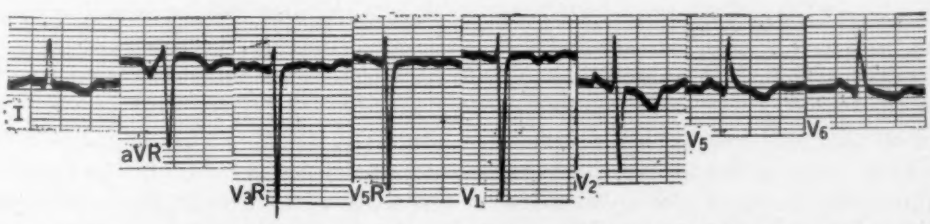


FIG. 42. Group 5. Partial transposition of the great vessels with pulmonic stenosis and ventricular septal defect. Electrocardiogram of a representative case (Case 41). $\hat{A}P$ directed downward and slightly forward and to the left (+80° in the frontal plane). The P wave has an increased amplitude and duration, more apparent in leads II, III and aVF, and is biphid in lead I and the precordial leads. $\hat{A}QRS$ is directed downward, backward and to the left, and $\hat{A}T$ points downward and to the right. There is a qR pattern with negative T wave in lead I, V_5 and V_6 and rS pattern in the right precordial leads.

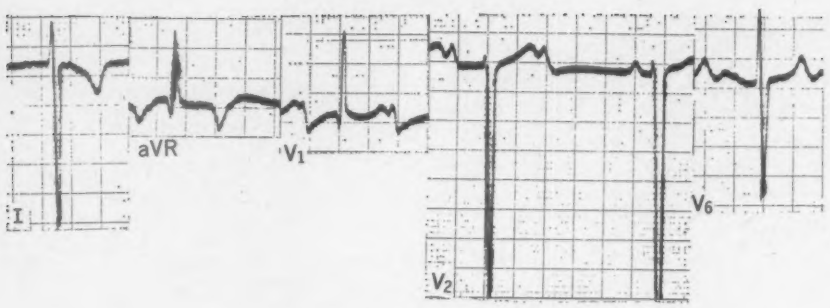


FIG. 44. Group 6. Single ventricle with pulmonic stenosis. Electrocardiogram of a representative case (Case 43). ÂP directed downward and to the left. High amplitude of the P wave especially in leads II, aVR and the middle precordial leads; increased duration reaching 0.14 second. Gross notches in all leads, with a well marked terminal notch. Diphasic P waves (with added independent notch) from V_4R to V_1 and biphid P waves in the left precordial leads. ÂQRS directed downward and to the right. ÂT directed almost vertically downward and slightly anteriorly. In aVR there is a qR pattern with negative T wave. In the precordial leads there are qR complexes from V_6R to V_1, suddenly changing to rS from V_2 onward. The T wave is positive in the right precordial leads (accompanying a high R wave).

sponding to the first three groups included in the usual concept of the tetralogy of Fallot [acyanotic (Case 32, Fig. 39), classic (Case 1, Fig. 35) and extreme tetralogy (Case 25, Fig. 37)] show a gradual transition in the vectorcardiographic alterations typical of right ventricular preponderance; namely, the initial vectors oriented anteriorly in the first two cases point backward in the third one, the terminal vectors are directed upward, backward and to the right in the first example, to the right in the second, and forward, downward and to the right in the third one; the main portion of the QRS loop is equally distributed on both sides of the zero point in the acyanotic patient and is more clearly displaced to the right in the other two. At the same time, the sagittal loop becomes more anterior and less inferior in these same two cases. In the first two cases the loop corresponding to repolarization is within normal limits (although it diverges clearly from the QRS loop in Case 1) while in the third example (extreme tetralogy of Fallot) it is distinctly directed backward so that it is almost diametrically opposed to the QRS loop in the horizontal projection. True spatial opposition (as we have noted in cases of pure pulmonary stenosis) was never observed.

Group 4: The representative case of group 4 (Case 37, Fig. 41) is vectorcardiographically similar to the example of classic tetralogy.

Group 5: The vectorcardiogram of a case in group 5 (Case 41, Fig. 43) shows the features of right ventricular preponderance (predominantly oriented downward, forward and to the right) but presents certain peculiarities; namely, initial invasion of the upper, left and anterior octant, the "figure of eight" configuration in all plane projections, the predominantly counterclockwise rotation in the horizontal projection and the abnormal spatial orientation of the T loop, which points downward and forward and is concordant with the QRS loop. The remarkably abnormal P loop was interpreted as representing right preponderance and disturbance in intraatrial conduction.

Group 6: The vectorcardiogram of the patient representing the last group (Case 43, Fig. 45) is frankly abnormal and difficult to interpret. Its shape and direction are very unusual and differ from those usually observed in left or right ventricular preponderance. Considering the anatomic position of the heart and the underlying malformation, we note that this vectorcardiogram corresponds to right ventricular electrical preponderance with the activation loop rotated between 90° and 180° (Fig. 46) on a longitudinal axis. In the latter case it would be similar to the tracing reproduced in Figure 37 (not considering the repolarization loop).

ELECTROCARDIOGRAPHIC ANALYSIS

The electrocardiographic records of forty-three cases in this series have been studied (Table II). All showed normal sinus rhythm.

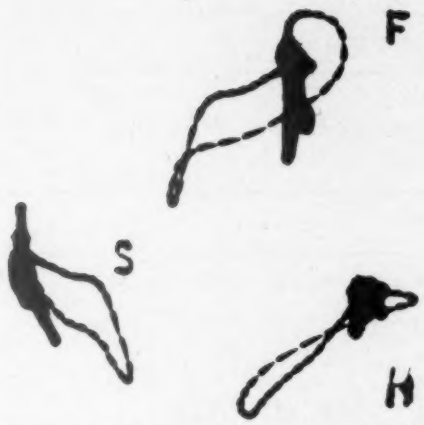


FIG. 45. Group 6. Single ventricle with pulmonic stenosis. Vectorcardiogram of a representative case (Case 43). The P loop, of unusual size and directed downward and slightly forward, is slowly inscribed and irregularly shaped; there is a more irregular and slower terminal portion which suggests an intraatrial conduction block. The QRS loop, elongated and predominantly directed forward, downward and to the right, is of abnormal configuration and in the last 0.02 second, is more slowly inscribed. The initial vectors go straight upward and the initial portion of the loop invades the upper left and anterior octant; its main portion is oriented anteriorly, inferiorly and to the right. The terminal vectors which coincide with the centripetal limb, point downward, forward and to the right. The loop rotates clockwise in the frontal plane, counterclockwise in the sagittal plane and draws a "figure of eight" in the horizontal plane. The very elongated T loop is directed downward and slightly forward; although diverging from the activation loop, the deviation is slight.

Seventeen patients had right atrial electrical preponderance, probably biatrial in four. In five patients of groups 1 and 2 the P waves were usually high and peaked in leads II, III, aVF and the right precordial leads. The biatrial pattern was observed in three cases of classic tetralogy and probably in one case of single ventricle where it coexisted with an atrial block. Atrioventricular conduction was normal in all cases except in Case 43 (single ventricle) when the P-R interval was 0.24 second. In the majority of cases (thirty-five patients) the mean ventricular electrical axis was oriented toward the lower right quadrant (+90° to +179°). The remaining eight cases were distributed as follows: three in the lower left quadrant (0° to +89°), two in the upper left quadrant (−1° to −90°) and three in the upper right quadrant (−91° to 180°).

In thirty-three of thirty-six cases covered by the current concept of the tetralogy of Fallot (groups 1, 2 and 3 of our classification) the mean ventricular electrical axis was confined to the lower right quadrant; in the remaining three, the clinical diagnosis could not be established beyond doubt in two, and the third had an associated subaortic stenosis. In three of the seven cases of the other groups (groups 4, 5 and 6 of our classification), the mean ventricular electrical axis pointed to the lower right quadrant (two were cases of single ventricle); the remaining four were more or less evenly distributed in the other quadrants. In two patients of group 4 the mean ventricular electrical axis was directed to the upper left quadrant and, in the two cases of group 5, it pointed in one to the upper left quadrant and in the other to the lower left one.

Right Precordial Leads: The positive deflection was predominant in the right precordial leads of nearly all cases. In four cases belonging to different groups (group 1, Case 13; group 3, Case 36; group 4, Case 39; group 6, Case 42) the negative deflection was larger (rS pattern) in V_1. Ten cases (seven in group 1, two in group 2 and one in group 6) showed qR or qRs patterns in the right precordial leads.

Six cases had a second positive deflection (rsR′ or rR′s) in V_1 usually referred to as the "incomplete right bundle branch block" pattern. The vectorcardiographic study of these cases always confirmed the existence of right ventricular electrical preponderance without any disturbance in intraventricular conduction.

The duration of the QRS complex, measured in lead II, was not greater than 0.08 second, except in two cases with durations of 0.10 second (Case 42, group 6; Case 11, group 1). In all cases showing rR′ or rsR′ pattern the duration of the QRS was equal to or less than 0.08 second.

All cases showed a sharp transition from V_1 to V_2, from predominantly positive to predominantly negative deflections. Ten cases were included in group 1 and 2; the other case belonged to group 6. In the left precordial leads (V_5 and V_6) persistence of S waves (with the R/S ratio less than or equal to 1) was found in twenty cases.

T Waves: In the majority of cases the mean electrical axis of ventricular repolarization pointed to the lower left quadrant (0° to 89°)

TABLE II
Electrocardiograms

Case No.	Sex	Age (years)	ÂP		ÂQRS		QRS					ÂT	
			Frontal Plane	Horizontal Plane	Frontal Plane	Horizontal Plane	Lead I	aVR	V_6R to V_3R; V_2 to V_6	V_1	V_6	Frontal Plane	Horizontal Plane
							A. Tetralogy of Fallot (Classic)						
1	M	5	+60°	AL	+135°	R	rS	qR	qR in V_6R and V_3R; R in V_4R; rS in V_2; RS in V_4 to V_6	R_3	rS	+55°	L
2	M	4	+60°	A	+150°	A	qRS	QR	rR's in V_3R; rS from V_2 to V_5; qRS in V_6	rR's	qRS	+50°	aL
3	F	3	+75°	aL	+120°	AL	rS	QR	qR_3 in V_3R; RS from V_2 to V_4; qR in V_6	qR_3	qR	+85°	AL
4	M	11	+50°	AL	+130°	pR	rS	R	qR from V_6R to V_3R; rS from V_2 to V_6	qR_3	rS	−30°	AL
5	M	18	+35°	AL	+110°	AR	rS	QR	qR from V_6R to V_3R; R_3 from V_2 to V_7	qR_3	RS	+60°	PL
6	M	14	+70°	A	+125°	R	rS	rSR'	qR in V_6R; R in V_5 and V_4R; rS from V_2 to V_7	R_3	RS	+60°	aL
7	M	19	+65°	AL	+135°	AR	qrS	qR	rsR' in V_4; rS in V_2 and V_3; RS from V_4 to V_5	rsR'	RS	+25°	aL
8	F	7	+5°	AL	+120°	aR	RS	QR	R from V_3 to V_4; R_3 in V_5; RS in V_6 and V_7	rR'	RS	0°	aL
9	M	13	...	...	+135°	R	rS	QR	R_3 from V_2 to V_6	R	R_3	+50°	AL
10	M	5	...	...	+120°	R	RS	rsr'	RS in V_2; R_3 in V_3 and V_4	RS	...	+70°	AL
11	M	17	...	...	+150°	...	rS	rS	R_3R's' in V_3; RS from V_3 to V_6	R	qRS	+60°	...
12	M	2	+40°	AL	+165°	R	rS	qR	rS from V_2 to V_6	R	RS	0°	L
13	M	5	+30°	AL	+150°	PR	qrS	rsR'	rS from V_2 to V_6	rS	rS	+45°	aL
14	F	3	+50°	AL	+140°	AR	rS	qR	rR's in V_2; rS from V_3 to V_6	R's	rS	+30°	AL
15	M	8	+45°	...	+150°	...	rS	qR	...	...	...	+45°	...
16	M	9	...	...	+100°	A	RS	rSR'	R in V_2; R_3 from V_3 to V_5; RS in V_6	R	RS	45°	Al
17	F	20 (months)	...	...	+140°	...	rS	...	rsr's' in V_2; rS in V_3	rsR'	...	−20°	...
18	F	2, 5	+50°	AL	+140°	AR	rS	qR	R_3 in V_2; RS from V_4 to V_6	R_3	RS	+45°	AL
19	F	12	+30°	AL	+120°	AR	rS	QR	RS from V_2 to V_6	R	RS	+30°	AL
20	M	15	+80°	AL	+130°	AR	qrS	rSR	RS from V_2 to V_5; qRS in V_6	R	qRS	+35°	AL
21	F	11	...	...	+160°	R	rS	qR	qRS in V_2; RS from V_3 to V_6	qR	RS	+120°	PL
22	M	10	+120°	...	+120°	A	rS	QR	rS in V_2; RS in V_4; qR_3 from V_5 to V_7	R_3	qRS	+45°	...
23	M	2	+90°	A	−160°	pR	qrS	qR	rS from V_2 to V_6	R_3	rS	+30°	L
24	F	11	+30°	AL	+135°	AR	qrS'	rsR'	R_3 in V_3R; rS from V_2 to V_5; qrS in V_6	R_3	qrS	...	...

in the frontal plane. In four cases (two of group 1 and two of group 2) it occupied the upper quadrant, diverging widely from the QRS axis (+150°). In another four cases (two of group 5, one of group 1 and one of group 6) the mean axis of repolarization was situated in the lower right quadrant.

In the precordial leads the T wave was predominantly oriented anteriorly and to the left in almost all cases. In three cases (two of group 1 and one of group 2) it was directed backward and to the left and in one case (group 5) backward and to the right.

Summary of Electrocardiographic Findings: Analysis of the electrocardiograms of the thirty-two cases established that the most common type is characterized by predominance of positive deflections in the right precordial leads (almost always a single positive deflection, occasionally accompanied by an R' or r'); a sharp transition between V_1 and V_2, a diphasic complex or predominance of the terminal negative deflection in V_5 or V_6 and marked right axis deviation in the frontal plane not exceeding +179°. Within the groups covered by the usual concept of the tetralogy of Fallot (groups 1, 2 and 3), only two

TABLE II *Continued*
Electrocardiograms

Case No.	Sex	Age (years)	ÂP		ÂQRS		QRS					ÂT	
			Frontal Plane	Horizontal Plane	Frontal Plane	Horizontal Plane	Lead I	aVR	V_5R to V_3R; V_2 to V_6	V_1	V_6	Frontal Plane	Horizontal Plane
							B. Tetralogy of Fallot (extreme)						
25	M	5	+50°	AL	+110°	AR	rS	rsS	qRs in V_2R; qRS in V_2; RS from V_3 to V_6	qRs	RS	−20°	PL
26	F	7	−15°	AL	+135°	AL	rS	QR	R in V_5R; Rs from V_5R to V_3R	RS	qR	0°	AL
27	M	5	+20°	AL	−170°	AR	rS	qR	Rs from V_2 to V_4; rS in V_5 and V_6	qR	rS	+65°	aL
28	M	1	+50°	AL	+100°	A	RS	QR	...	rR′	RS	+80°	AL
29	F	11 (months)	+55°	AL	+105°	⊥	rS	QR	Rs in V_2 and V_4; rS in V_6	Rs	RS	+70°	AL
30	M	15	...	...	+130°	RA	rS	rSR′	RS from V_2 to V_6	Rs	rS	−20°	AL
31	F	10	+80°	...	+175°	...	QS	R	R in V_3R; RS in V_2; rS from V_3 to V_5	Rs	rS	+15°	...
							C. Tetralogy of Fallot (mild or acyanotic)						
32	F	19	+50°	A	+135°	R	rS	QR	Rs in V_3R; RS from V_2 to V_6	Rs	RS	+70°	AL
33	F	16	+50°	AL	+135°	AR	rS	qR	qR in V_4R and V_3R; Rs in V_2 and V_3; RS in V_4 and V_7	qR	RS	+10°	PL
34	M	11	+45°	L	+60°	L	qRr′	rSr′	rS from V_2 to V_4; qRs in V_5; qR in V_6	RS	qR	+55°	AL
35	F	6	...	...	+120°	R	rS	qR	Rs in V_4R; RS in V_2; Rs from V_3 to V_5	Rs	R	+50°	AL
36	M	9	+40°	A	+75°	PL	Rs	rS	rS in V_4; qRs from V_5 to V_6	rS	qR	+45°	aL
							D. Interventricular Septal Defect and Pulmonary Stenosis						
37	F	25	+60°	L	+120°	AR	RS	QR	R in V_3R; Rs from V_2 to V_5; RS in V_6	R	RS	+30°	PL
38	M	37	+60°	AL	0°	A	Rs	Qr	rsR′ in V_4R; Rs from V_3R to V_5; R in V_6	Rs	R	+20°	...
39	F	7	+45°	A	−75°	...	qR	qR	rS in V_4R; qrS in V_2; qRS V_3 to V_5; rS from V_6 to V_8	rS	rS	+80°	AL
							E. Transposition (or Pseudotransposition) of the Great Vessels and Interventricular Septal Defect and Pulmonary Stenosis						
40	M	6	+120°	AR	−90°	A	QR	qRS	rS from V_6R to V_3R; rR′ in V_2 and V_4; rsr′ V_5 to V_8	RSr′	rSR′	+135°	AR
41	M	7	+80°	A	+60°	AL	qR	rS	rS from V_5R to V_3R	rS	qR	+100°	PR
							F. Single Ventricle and Pulmonary Stenosis						
42	M	16	+30°	AL	+100°	pL	RS	Qr	rsR′ in V_4R; rS in V_3R; rS in V_2 and V_3R	rS	Rs	0°	AL
43	F	27	+60°	AL	+135°	R	rS	qR	qR from V_6R to V_3R; rS from V_2 to V_7	qRs	rS	+95°	aL

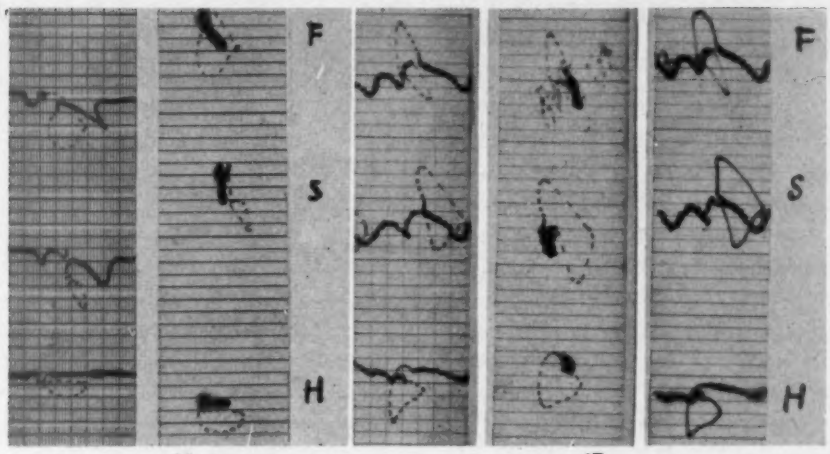
Note: In this table and Table III, abbreviations are as follows: A = anterior; P = posterior; I = inferior; S = superior; L = left and R = right. Lower case letters indicate small amplitude of deflection.

patients (both from group 3, one of them having associated aortic stenosis) could not be included in this common type. The majority of the electrocardiograms revealed no evident alterations of ventricular repolarization of the type usually called "ventricular strain." Contrary to what was expected for these patients' average age, positive T waves in the right

TABLE III
Vectorcardiograms

Case No.	Sex and Age (years)	P Loop Octant	QRS Loop						T Loop Octant
			Horizontal Plane	Sagittal Plane	Frontal Plane	Octant	Initial Vectors	Terminal Vectors	
			A. Tetralogy of Fallot (classic)						
1	M 5	AI	cw.*	c. cw.†	cw.	AIR	ASR	AR	IL
2	M 4	AIL	cw.	c. cw.	cw.	AISLR	A	PSR	AIL
3	F 3	AI	cw.	cw.	cw.	AI	AS	PI	AIL
4	M 7	I	cw.	c. cw.	cw.	IR	AS	...	± circular
6	M 14	AIL	cw.	(Fig. of 8)	cw.	AILR	ASR	PIL	AIL
7	M 19	AI	cw.	c. cw.	cw.	AILR	AL	IR	IL
8	F 7	AI	cw.	c. cw.	cw.	ARsI	AS	PLS	Ip
9	M 13	...	cw.	c. cw.	cw.	AILR	...	AIR	IL
20	M 14	I	cw.	c. cw.	cw.	AILR	S	ASR	IL
24	F 11	I	cw.	c. cw.	cw.	ARsi	LI	ASL	IL
22	M 10	AIL	cw.	c. cw.	cw.	AILR	AS	R	AIL
			B. Tetralogy of Fallot (extreme)						
25	M 5	AI	cw. (Fig. of 8)	c. cw.	cw.	AIR	PSL	AIR	PIL
26	F 7	AIL	c. cw. cw.	cw.	cw.	AIL	ASR	AI	AIL
31	F 9	I	cw. (Fig. of 8)	cw.	c. cw.	ARi	AS	PL	LpI
			C. Tetralogy of Fallot (mild or acyanotic)						
32	F 19	I	cw.	c. cw.	cw.	ArISR	AIL	PSR	IL
34	M 11	AIL	c. cw.	cw.	c. cw.	APIL	AR	PSL	IL
35	F 6	...	cw.	cw.	cw.	AI	...	...	AI
36	M 9	AIL	c. cw.	cw.	cw.	AILr	ASr	AIL	IL
			D. Interventricular Septal Defect and Pulmonary Stenosis						
33	F 17	I	cw.	c. cw.	cw.	AILR	AIL	AIR	PIL
37	F 2.5	AI	cw.	c. cw.	cw.	AIR	AS	AIR	IL
38	M 37	AI	cw.	(Fig. of 8)	cw.	AIL	AI	AIR	IL
39	F 7	...	cw.	c. cw.	cw.	APSR	AIL	PSR	IL
			E. Transposition (or Pseudotransposition) of the Great Vessels and Interventricular Septal Defect and Pulmonary Stenosis						
41	M 7	I	cw. (Fig. of 8)	cw.	c. cw.	APIL	AS	PIR	AI
			F. Single Ventricle and Pulmonary Stenosis						
42	M 16	AI	c. cw.	cw.	cw.	PILR	I	PIR	IL
43	F 27	I	(Fig. of 8)	c. cw.	cw.	ARi	SL	PL	Il

* cw. = clockwise; † c. cw. = counterclockwise.



46 47

FIG. 46. Vectorcardiogram (Case 38). The QRS loop predominantly occupies the lower, left and anterior octant.
FIG. 47. Vectorcardiogram (Case 2). The QRS loop is situated to the left and to the right of the isoelectric point.

precordial leads were relatively frequent.

In half of the cases the P waves were peaked in leads II, III, aVF and the right precordial leads, with right deviation of ÂP in the frontal plane. The variety of patterns in each particular lead makes it difficult to establish any consistent progression of the electrocardiographic alterations within this series. We did not note any evident correlation between the variations of the commonest type of electrocardiogram and pathophysiologic groups of our classification.

The consistent finding of right ventricular preponderance, generally less marked than that observed in cases of pulmonary stenosis both pure and associated with interatrial septal defect, leads us to consider the electrical alterations of significant diagnostic value in cases of complexes of the Fallot type. In the absence of right ventricular electrical preponderance this diagnosis (as the only malformation present) should be considered cautiously.

VECTORCARDIOGRAPHIC ANALYSIS

Only twenty-five of the forty-three cases could be studied vectorcardiographically (Table III). Detailed analysis of these vectorcardiograms permit grouping twenty cases within a frequent morphologic type with some variation of spatial distribution as will be shown. The remaining five cases with quite different features could not be included in any homogeneous group. They varied from a normal example (Case 34, interventricular septal defect plus infundibular pulmonary stenosis) to the remarkable alterations found in Case 39 (pulmonary stenosis plus interventricular septal defect and possibly interatrial septal defect and/or anomalous venous return) where it was similar to cases of "ostium primum" because of the upward direction and counterclockwise rotation of the QRS loop in the frontal plane. The alterations shown by Case 41 (pseudotransposition of the great vessels with inversion of the ventricular chambers) were also very peculiar. These five atypical cases also include two patients with single ventricle (Cases 43 and 42) who differed from one another. The orientation was predominantly anterior in the first patient and posterior in the other. In the twenty vectorcardiograms grouped on the basis of their common morphology the activation loops were always oriented anteriorly and inferiorly. The repolarization loop was frequently divergent but never spatially opposed. The initial vectors were almost always directed anteriorly and upward and the terminal vectors were, in the majority of cases, oriented to the right, indifferently forward or backward.

QRS Loops: Looking at the activation loops confined to the anterior and inferior octants we can establish a gradation in keeping with the relative size of the areas occupied to the right and to the left of the zero point. Thus in four cases (Cases 38, 26, 3 and 36) the loop predominantly occupies the lower left and anterior octant (Fig. 46); in two cases (cases 32 and 2) the areas situated to the left and to the right of the zero point were comparable (Fig. 47); in another three (Cases 4, 24 and 31) the QRS loop was almost totally to the right of the isoelectric point (Fig. 48); in the remaining eleven cases (Cases 1, 6–9, 20, 22, 25, 33, 35 and 37) it was situated to the right of

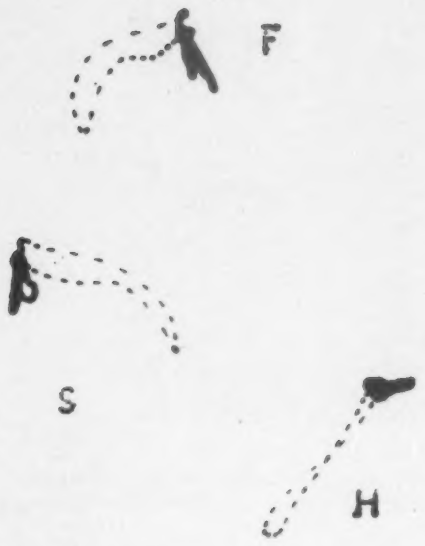


FIG. 48. Vectorcardiogram (Case 31). QRS loop was almost totally to the right of the isoelectric point.

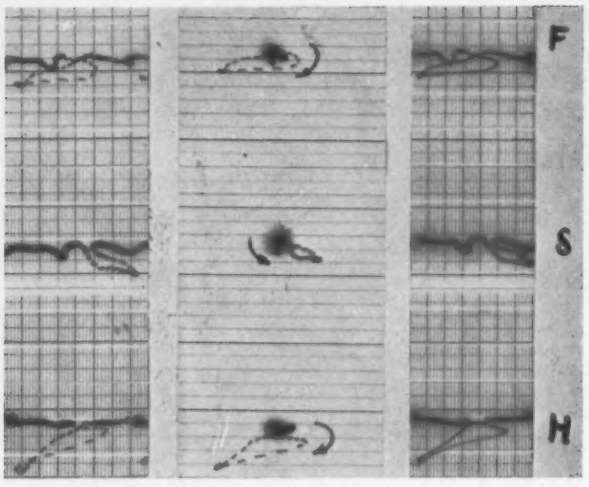


FIG. 49. Vectorcardiogram (Case 33). The QRS loop is situated predominantly to the right of the isoelectric point, with a considerable initial portion on the left side.

the zero point but always with a considerable initial portion on the left side (Fig. 49).

In eighteen of these twenty cases the QRS loop rotated clockwise in the horizontal and frontal projections; in the majority of patients the rotation was counterclockwise in the sagittal projection (clockwise in four). Of the remaining two cases, the rotation was counterclockwise in the horizontal plane, clockwise in the other two planes in Case 36; in the other patient (Case 31) the horizontal projection adopted a "figure of eight" contour, the rotation being clockwise in the sagittal and counterclockwise in the frontal planes. Of these two cases which did not rotate clockwise in the horizontal projection, one had extreme tetralogy of Fallot with pseudotruncus (Case 31) and the other, acyanotic tetralogy of Fallot associated with subaortic stenosis (Case 36).

Significance of Findings: We may conclude that with rare exceptions both the vectorcardiogram and the electrocardiogram showed a good homogeneity, specially in the first three groups, with clear predominance of the electrical forces directed anteriorly, inferiorly and to the right and without spatial opposition of the repolarization loop. The variations could not be consistently correlated with the clinical severity. From current electrocardiographic criteria it is sometimes difficult to ascertain if some of the patterns correspond to physiologic preponderance of the right ventricle (in the youngest patients) or to disturbances in intraventricular conduction (in cases with a second positive deflection in the right precordial leads). The vectorcardiographic study was of paramount importance in interpreting these dubious cases because, on the basis of our previous experience, all of them could be interpreted as representing pathologic preponderance of the right ventricle.

HEMODYNAMIC FINDINGS

Of the forty-three cases, thirty-five were studied by venous catheterization (Table IV). The average age of the patients submitted to hemodynamic examination was eleven years (oldest, 37; youngest, 1). Only two were more than twenty years old. In the majority of cases the catheter was introduced through an antecubital vein and through one of the saphenous veins when angiocardiographic examination was carried out simultaneously.

Only in eight cases (group 1, 2 and 3) did the catheter enter the aorta from the right ventricle; two patients (Cases 33 and 32) belonged to the acyanotic group and the diagnosis could be established by that fact. The catheter entered the left ventricle through an interventricular septal defect in only one case (Case 36). In six cases the catheter passed from the right atrium to the left atrium. An increase of the oxygen concentration greater than 1.5 volume per cent at the level of the right atrium allowed the presumptive diagnosis of true interatrial septal defect in four cases. Cardiac catheterization demonstrated anomalous drainage of the pulmonary veins in three

cases and, in another two cases, a left superior vena cava entering the right atrium.

Pulmonary capillary pressure recorded in eight cases showed mean values ranging from 5 to 12 mm. Hg. In four patients it exceeded the upper limit of normal, 8 mm. Hg. This finding may be related to the existence of bronchopulmonary arterial shunts.

Pulmonary Artery and Right Ventricular Pressures: The catheter entered the pulmonary artery in twenty-one patients. Such passage was more difficult in extreme tetralogy of Fallot (group 2) and we could insert the catheter into the pulmonary artery in only one of the five cases. This was possible in more than half the patients of group 1 (thirteen out of twenty), in almost all cases of group 3, and in two of group 4.

The average pulmonary artery pressure was normal [19/9 (13) mm. Hg] but the pressures in the different groups varied. For instance, in cases of slight or acyanotic tetralogy of Fallot the average pressures were higher [25/12 (20) mm. Hg] than in cases of group 1 covering classic tetralogy of Fallot [16/8 (11) mm. Hg]. In this study of the right ventricular and pulmonary artery pressures some of the initial cases were not included (Cases 17, 21, 23, 28 and 30), as in these patients pressures were recorded by a water manometer recording only the mean pressures.

The existence of an infundibular chamber could be demonstrated hemodynamically in four of twenty-one cases in which the catheter entered the pulmonary artery. However, only in fourteen of the twenty-one patients could the transition curves be properly analyzed. The analysis of the pressure gradients enables us to establish that in one of these patients the stenosis was exclusively infundibular. Right venticular systolic pressure never exceeded 130 mm. Hg and only in eleven cases was it equal to or greater than 100 mm. Hg. The lowest pressure recorded was 38 mm. Hg. The average systolic pressure was 88 mm. Hg. There was no significant variation from group to group except in group 2 in which pressures were markedly higher.

In nine cases the intraventricular end diastolic pressure slightly exceeded the upper limit of normal. None presented any subjective or objective clinical manifestiation of congestive cardiac failure. The mean atrial pressure also slightly exceeded the upper limit of normal in ten subjects.

In the fourteen patients in whom the pulmonary artery-right ventricular systolic gradient could be determined, an average gradient of 72.5 mm. Hg (maximum of 107 mm. Hg) was noted. Only in three cases was the gradient equal to or less than 40 (in one case only 12 mm. Hg). In the eight patients in whom the catheter could enter the aorta from the right ventricle, the intra-aortic systolic pressure was similar to the right ventricular systolic pressure (maximum difference of 6 mm. Hg in one case).

Morphology of the Pressure Curves: The pulmonary pressure curve was frequently atypical, showing multiple oscillations; at other times, a late systolic wave with a slow rise could be recognized. The right ventricular pressure curve often showed symmetrical limbs and a "damped" appearance. In several cases alterations in the pulmonary artery–ventricular transition have been found which are currently attributed to the so-called "Venturi effect." A predominant, sometimes a giant, *a* wave was found in the right atrial curve in the great majority of cases.

Shunts: The average arterial oxygen saturation was 78.5 per cent in group 1, 62 per cent in group 2 and varied between 90 and 92 per cent in group 3. Blood samples from the right ventricle showed an increase of the oxygen concentration equal to or greater than 1 volume per cent in eight of the twenty cases of group 1, in two of the five cases of group 2 and in two of the five cases of group 3. Among groups 1, 2 and 3 there was no difference in the frequency with which the existence of a left to right shunt at the ventricular level could be demonstrated.

In one of the two cases in group 4 a left to right shunt at the ventricular level was noted. One of the two cases of single ventricle showed an increase in the oxygen concentration at the ventricular level, reaching 4.8 volumes per cent.

Comments

The correct interpretation of the clinical signs supplied by physical examination, complemented by fluoroscopy, phonocardiography, electrocardiography and vectorcardiography, permits the diagnosis of complex of the Fallot type in the majority of cases. Angiocardiography and venous catheterization provide more exact anatomic and pathophysiologic knowledge of this syndrome. Dye dilution curves and isotopically labeled substances facilitate the study of shunts. Angiocardiographic, electrical and hemodynamic data ex-

TABLE IV
Hemodynamic Data

Case No.	Sex	Age (years)	Pressure (mm. Hg)					
			Aorta	Pulmonary Artery Wedged	Pulmonary Artery	Infundibular Chamber	Right Ventricle	Right Atrium
								A. Tetralogy of
1	M	5	...	...	...	...	55/2	8/4(6)
2	M	4	...	...	...	...	78/10	(6)
3	F	3	...	...	...	...	46/10	...
4	M	11	116/105	(10)	(14)	...	121/10	(10)
5	M	18	...	7/3(5)	23/7(14)	...	130/4	10/2(6)
6	M	14	...	...	15/10(12)	30/8	70/4	8/2(4)
7	M	19	...	8/5(7)	11/6(9)	...	105/5	(2)
8	F	7	...	...	15/10(12)	...	80/0	10/0(4)
9	M	13	...	...	18/6(8)	...	120/−2	...
11	M	17	...	...	(7)	...	(54)	(3)
12	M	2	...	...	14/6(9)	...	90/2	(6)
13	M	5	...	...	(12)	...	80/5	(5)
16	M	9	...	...	(15)	...	(45)	(4)
17	F	20 (months)	...	...	(24)	...	(50)	...
20	M	15	...	...	(10)	...	100/2	(5)
21	F	11	...	...	(9)	...	(50)	(9)
23	M	20	...	...	...	...	(40)	(10)
24	F	11	73/53(59)	...	...	...	70/7	11/6(9)
22	M	10	...	...	...	...	96/0	6/2(4)
								B. Tetralogy of
25	M	5	...	...	...	...	75/5	15/7(10)
26	F	7	96/67	(11)	17/11(14)	40	100/9	7/−2(5)
28	M	1	...	...	...	...	(33)	(7)
30	F	15	...	...	...	...	(44)	(12)
31	F	9	77/49	...	...	...	71/15	12/8(10)
								C. Tetralogy of Fallot
32	F	19	110/60(80)	(7)	28/10(16)	...	110/7	10/0(5)
33	F	16	120/72	10/2(6)	18/8(9)	25/0	120/8	11/−2(4)
34	M	11	...	...	26/16(22)	...	38/3	9/6(7)
35	F	6	...	...	...	...	98/10	18/12(15)
36	M	9	75/6(LV)	...	26/13(21)	29/4	66/0	8/4(6)
								D. Interventricular Septal
38	M	37	...	20/9(12)	29/13(20)	...	100/10	12/3(8)
39	F	7	...	13/6(9)	20/11	...	59/5	12/0(5)
								E. Transposition (or Pseudotransposition) of the Great
40	M	6	83/70	...	...	...	85/5	10/3(6)
41	M	7	80/50(65)	...	...	...	85/17	(16)
								F. Single Ventricle
42	M	16	...	...	15/5(8)	...	110/10	(5)
43	F	27	...	...	...	57/13	125/10	17/4(13)

TABLE IV *Continued*

Oxygen (vol. per cent)							
Superior Vena Cava	Inferior Vena Cava	Right Atrium	Right Ventricle	Pulmonary Artery	Aorta	Radial Artery	Arterial Saturation (per cent)
Fallot (classic)							
15.9	16.5	16.1	17.1	...	...	...	...
14.5	14.9	14.5	14.6	...	...	....	...
9.4	8.5	9.8	8.0	...	...	...	...
11.7	...	13.8	12.3	12.1	19	...	76
16.9	17.2	18.7	18.8	19.1	...	25.5	83
18.1	19.7	19.5	19.1	...	27.0	...	Aorta 85
23.8	...	22.9	24.2	22.0	...	27.6	87
14.4	12.2	14.4	16.2	17.6	...	20.5	86
14.3	12.5	14.1	15.8	15.8	...	18.7	89
13.9	...	14.2	13.9	13.5	...	18.5	75
...	9.3	10.6	10.6	10.2	...	14.8	75
13.1	11.9	12.4	14.8	13.4	...	15.5	75
11.7	...	11.4	12.3	...	18.1	17.6	69
8.7	...	10	10.9	...	...	15.5	67
16	...	16	17.5	...	...	20.4	78
21	24.8	23.6	25.8	25.8	...	26.9	80
15.3	11.5	17	16	...	...	19.6	79
14.9	...	19.2	18.6	...	18.9	...	...
14.6	14.2	15	17.2	...	...	18.2	79
Fallot (extreme)							
14.9	14.7	14.4	16.0	...	...	...	...
...	...	9.7	8.5	7.8	14.5	...	Aorta 67
7.4	7.9	...	...	...	...	13.5	61
18.2	...	18.3	20.9	...	...	...	...
16.4	...	16.6	17.5	...	20.3	...	69
(mild or acyanotic)							
13.4	...	15.6	17.1	16.6	19.4	...	Aorta 92
13.1	13.6	13.0	14.5	13.8	19.6	19.8	92
15.3	...	15.7	16.2	16.5	...	...	96
10.6	13.0	11.0	11.8	...	...	16.2	90
9.4	9.6	9.9	10.2	11.0	13.8(LV)	13.6	94
Defect and Pulmonary Stenosis							
13.4	...	13.5	14.6	14.8	...	17.9	92
13.8	14.3	14.3	14.1	14.3	...	...	...
Vessels and Ventricular Septal Defect and Pulmonary Stenosis							
16.5	16.8	16.2	15.9	...	22	22.1	85
15.0	15.4	15.8	16.0	...	19.2	...	Aorta 80
and Pulmonary Stenosis							
...	....	20.3	21.4	21.7	...	23.0	76
12.4	12.8	13.8	18.3	...	...	17.7	83

plain the variability of the symptoms within each group of the complex of the Fallot type. However, in the first four groups the physical signs are not as characteristic as in pure pulmonary stenosis; precordial bulging is not as frequent; the systolic murmur is, as a rule, less intense or even absent in severe cases. When valvular and infundibular stenosis coexist in any of the four groups the systolic murmur is louder in the third and the fourth left interspaces and may start immediately after the beginning of systole. As the right ventricle empties easily the systole is not prolonged and the murmur is not so long as in pure pulmonary stenosis.

When a collateral circulation is established through the bronchial arteries, a continuous murmur may be heard over the two lung fields. The second sound is sometimes accentuated in the second left interspace; phonocardiography reveals that such accentuation depends only on the closure of the aortic valves. The second sound is clearer because of the anterior position of the aorta. The poor pulmonary circulation and the low pulmonary pressure lessen the pulmonary component of the second sound. The electrical and hemodynamic patterns of right ventricular hypertension are less conspicuous than in cases of pulmonary stenosis either pure or associated with interatrial septal defect.

The pathophysiologic interpretation of the complex of the Fallot type must account for the following three functional conditions: (1) interventricular septal defect and slight valvular or infundibular pulmonary stenosis associated with left to right shunt; (2) interventricular septal defect and moderate valvular or infundibular pulmonary stenosis associated with bidirectional shunt; (3) interventricular septal defect with slight valvular or infundibular stenosis associated with right to left shunt.

In classic tetralogy of Fallot (group 1) there is, as a rule, severe pulmonary stenosis and a large septal defect, but the septal defect may be moderate and the intensity of the pulmonary stenosis variable. Hemodynamic changes resulting from the combination of these factors consist of a large right to left shunt (sometimes associated with a small left to right shunt) and equal pressures in both ventricles. Varying clinical signs and symptoms of early cyanosis, squatting, clubbing and dyspnea depend upon those hemodynamic changes.

Extreme tetralogy of Fallot, suggested by Taussig[16] (group 2), consists of extreme stenosis or even atresia of the pulmonary artery associated with a large interventricular septal defect. It is characterized hemodynamically by a large right to left shunt, reduction or absence of the pulmonary blood flow and comparable pressures in both ventricles.

Slight tetralogy of Fallot (group 3) includes acyanotic patients and those slightly cyanotic on exertion. This form is characterized, anatomically, by a mild or moderate pulmonary stenosis associated with interventricular septal defect of small or moderate size. The blood volume shunted in either direction is small. Right intraventricular pressure may be equal to or lower than left intraventricular pressure. Symptoms are mild and cyanosis is absent at rest.[17–19] Rowe et al.[12] reported four acyanotic patients under the designation of "atypical tetralogy of Fallot." Keats et al.[20] described four cases without cyanosis. McCord et al.[15] and Holladay and Withman[21] also include the acyanotic cases in the tetralogy of Fallot. According to Wood et al.[22] this group constitutes 10 per cent of the cases of the tetralogy of Fallot.

In this combination of pulmonary stenosis and large interventricular septal defect, the size of the latter partly influences the position of the aorta and, thus, the cyanosis. In acyanotic or slightly cyanotic cases the aorta is only poorly opacified on angiocardiography and the direct passage of the catheter from the right ventricle into the aorta offers diagnostic aid.

Patients in group 4 show the clinical picture and the pathophysiologic signs of the tetralogy of Fallot but no overriding of the aorta.[23] Angiocardiography demonstrates the absence of aortic overriding. The clinical picture is conditioned by the large septal defect and severe pulmonary stenosis. When the surgical correction of these malformations consists only in a pulmonary valvulotomy, this syndrome becomes an interventricular septal defect with pulmonary hypercirculation and consequent right ventricular overloading. Right ventricular hypertrophy leading to clockwise rotation of the heart and dextroposition of the aorta may change this syndrome of the Fallot type into a classic tetralogy of Fallot.

Patients of this group demonstrated that pulmonary stenosis associated with interventricular septal defect may lead to a right to left shunt and cyanosis either with or without aortic overriding. Similar systolic pressures in both

ventricles make more intimate the relations between the aorta and the interventricular septal defect.

Partial transposition of the great vessels (group 5) is functionally comparable to classic tetralogy of Fallot in which a great portion of the blood expelled by the ventricles is shunted directly into the aorta. Cyanosis is precocious and intense, accompanied by clubbing and polycythemia.

The group of single ventricle (group 6) is formed by those cases in which the interventricular septal defect reaches its largest size, accompanied by pulmonary stenosis of variable degree. The admixture of venous and arterial blood and the degree of pulmonary stenosis determine the hemodynamic changes and the clinical picture.

The pathophysiology of cyanosis in the different groups of the complex of the Fallot type raises the problem of the location of the admixture of venous and arterial blood. Does it occur in both infundibular chambers, in the aorta or in the left ventricle, due to right ventricular hypertension and right to left shunt? The location of the venoarterial blood mixing depends on the interrelations of the following three factors: (1) degree of stenosis of the outflow tract; (2) size of interventricular septal defect; and (3) degree of aortic overriding. If the stenosis of the outflow tract is severe and aortic overriding absent or little pronounced, the mixture occurs predominantly in the left ventricular outflow tract and very slightly in the aorta. If the stenosis is moderate and aorta overriding severe the mixture occurs in the aorta and only partially in the infundibular chambers. The variation in the intensity of these three elements enables us to understand the variable pathophysiology of the cases covered by the complex of the Fallot type ranging from severe cyanotic conditions to the acyanotic group. Aortic overriding is not the dominating factor in determining the hemodynamic pattern.

Summary

Clinical, angiocardiographic, electrocardiographic, vectorcardiographic and hemodynamic data concerning patients with tetralogy of Fallot showed that the tetralogy of Fallot must be regarded as a part of a large "spectrum" syndrome (the complex of the Fallot type) which includes the following six groups: (1) classic tetralogy of Fallot; (2) extreme tetralogy of Fallot; (3) acyanotic tetralogy of Fallot; (4) stenosis of the outflow tract of the right ventricle or pulmonary stenosis with interventricular septal defect and no overriding of the aorta; (5) partial transposition of the great vessels with stenosis of the outflow tract of the right ventricle or pulmonary stenosis and interventricular septal defect; (6) single ventricle with pulmonary stenosis. There is a common anatomic denominator: the existence of interventricular septal defect and stenosis of the right ventricular outflow tract or pulmonary stenosis. The groups differ from one another only in the anatomico-functional interrelations of these two factors. The third factor (aortic overriding) may be absent. All groups show a comparable clinical and pathophysiologic picture.

This report shows the results of the angiocardiographic, electrocardiographic, vectorcardiographic and hemodynamic studies in patients included in each group of the complex of the Fallot type which illustrate the respective pathophysiologic features.

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Reports on Therapy

The Diabetogenic Effect of Thiazide Diuretics*

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THE efficacy of chlorothiazide and its analogs as diuretic agents is well known.[1–3] These compounds have been used extensively and with remarkably few untoward reactions not specifically attributable to their diuretic effect, even following prolonged administration of large doses. Less known, and of considerable interest and potential significance, is their effect upon body metabolism and in particular that of carbohydrate. The purpose of this report is to emphasize that these compounds are sometimes diabetogenic.

MATERIAL AND METHOD

Twenty-five hospitalized ambulant patients were selected at random. There were nineteen women and six men, twenty-three to eighty-four years of age, with an average age of 59.8 years. Eight had coronary artery disease, seven cerebrovascular lesions, two rheumatic heart disease, one benign essential hypertension, one arteriosclerotic valvular heart disease, one hyperthyroidism, one pulmonary emphysema, one gastric diverticulum and three were normal. There was a history of diabetes mellitus in only one and no specific treatment was ever taken.

At the time of study and for at least one week previously, the diet was unrestricted and high in carbohydrate, and illness was stabilized.

A morning two hour postprandial specimen of blood was obtained for determination of glucose by the Folin-Wu method. In our laboratory, the two hour postprandial blood glucose does not exceed 120 mg. per cent in the normal. Blood specimens were obtained both with and without previous administration of chlorothiazide† or trichlormethiazide.‡ Breakfast was kept constant. The control value was that obtained on the day the drug was not administered. The following day, either chlorothiazide or trichlormethiazide was given orally with breakfast. Twelve received 8 mg. of trichlormethiazide, seven, 16 mg. of trichlormethiazide and six, 1,000 mg. of chlorothiazide. The drugs were well tolerated and no symptoms were produced.

RESULTS

The morning two hour postprandial blood glucose values on both the control day and the day of administration of either chlorothiazide or trichlormethiazide are given in Table 1.

Fifteen persons, ten women and five men, thirty-nine to seventy-four years of age with an average age of 59.2 years, demonstrated after administration of the thiazide compounds no rise of blood glucose to a value either greater than 120 mg. per cent, if initially normal, or greater than the control, if initially abnormal. The control value was 120 mg. per cent or less in six and greater in nine. Following thiazide administration, the blood glucose was 120 mg. per cent or less in eleven. In the remaining four, it exceeded this value but was less than the control in three and equalled it in one. Of the fifteen, eight received 8 mg. of trichlormethiazide, four, 16 mg. of trichlormethiazide and three, 1,000 mg. of chlorothiazide.

Ten persons, nine women and one man, twenty-three to eighty-four years of age, with an average age of 59.8 years, demonstrated after administration of the thiazide compounds blood glucose values greater than the control and

† Generously supplied as Diuril® by Dr. Edmund W. J. DeMaar, Merck, Sharp and Dohme, Inc.

‡ Generously supplied as Naqua by Dr. J. Black, Schering Corporation.

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TABLE I

Two Hour Postprandial Blood Glucose Values before and after Administration of Chlorothiazide or Trichlormethiazide

Case No.	Sex and Age	Diagnoses*	Two Hour Postprandial Blood Glucose (mg. %)		Compound Used†	Dose (mg.)
			Before	After		
1	F, 80	CAD	130	103	T	8
2	F, 69	CVA	90	113	T	8
3	F, 58	RHD	225	218	T	8
4	M, 39	N	96	103	T	8
5	M, 43	N	88	105	T	8
6	M, 42	CAD	133	133	T	8
7	F, 45	CAD	133	84	T	8
8	F, 73	GD	96	88	C	1,000
9	F, 49	CAD	141	123	C	1,000
10	F, 68	CVA	130	109	T	8
11	M, 70	PE	119	115	C	1,000
12	M, 72	N	133	130	T	16
13	F, 63	CVA	113	109	T	16
14	F, 74	CVA	189	84	T	16
15	F, 43	CAD	158	113	T	16
16	F, 63	HBP	141	162	T	8
17	F, 66	CAD	119	168	T	8
18	F, 84	ASHD	113	173	T	8
19	F, 72	CVA	107	152	C	1,000
20	F, 23	HT	127	152	T	8
21	F, 56	CAD	137	147	C	1,000
22	F, 50	RHD	137	207	T	16
23	F, 67	CVA	100	137	T	16
24	F, 63	CAD	212	218	T	16
25	M, 54	CVA	135	152	C	1,000

* CAD = coronary artery disease; CVA = cerebrovascular accident; RHD = rheumatic heart disease; GD = gastric diverticulum; PE = pulmonary emphysema; HT = hyperthyroidism; HBP = hypertension; ASHD = arteriosclerotic heart disease; N = normal.

† T = trichlormethiazide; C = chlorothiazide.

exceeding 120 mg. per cent (Cases 16 to 25). The control value was less than 120 mg. per cent in four. After thiazide administration these four showed a rise of blood glucose of 37 to 60 mg. per cent. The remaining six had control values exceeding 120 mg. per cent and showed after thiazide administration a rise of blood glucose of 6 to 70 mg. per cent. One of these six (Case 24), a sixty-three year old woman with coronary artery disease, knew of diabetes mellitus for eight years but had never received any specific treatment. She was the only one in the entire group with any knowledge of pre-existing diabetes mellitus.

COMMENTS

This study demonstrates that the administration of thiazide compounds is sometimes followed by an elevation of the two hour postprandial glucose exceeding 120 mg. per cent. Appearance or intensification of diabetes mellitus after institution of therapy with thiazide compounds has been noted by others.[4–6] Goldner, Zarowitz and Akgun,[5] in the only systematic study, observed in six of twenty diabetic persons an increase in hyperglycemia which occurred three to five days after initiation of treatment with thiazide compounds and disappeared soon after cessation of these drugs. None of their twenty nondiabetic persons showed an abnormally elevated blood glucose during thiazide therapy, or change in oral glucose tolerance test that was done in four both before and during medication. In the present study, administration of thiazide compounds was not followed by increased abnormality in nine with elevated control values or by rise to abnormal levels in six whose two hour postprandial blood glucose was initially normal.

In an additional three normal subjects, not

included in this report, three hour oral glucose tolerance tests with and without administration of 8 mg. of trichlormethiazide showed no significant differences. On the other hand, thiazide administration precipitated hyperglycemia in four and intensified it in six.

The mechanism of the production of hyperglycemia following thiazide administration is unknown. It was apparently not related to dose, which was variable, or to diuretic effect, for it appeared early before peak diuresis,[7] and occurred in the absence of diuresis. It is also not due to electrolyte depletion for again it is early in appearance and no change has been found in blood electrolytes including potassium.[5] Moreover, it is not due to interference with insulin or oral hypoglycemic agents for it occurs in their absence, and administration with hypoglycemic agents is not necessarily followed by a worsening of the diabetic state.[8] Finally, although a toxic pancreatic effect has been reported following prolonged use of thiazide compounds in middle-aged or elderly persons,[9] such an effect here is unlikely because hyperglycemia occurred early, regardless of age and without accompanying change in occasional determinations of serum amylase.

Its importance at the moment resides in the fact that thiazide compounds can produce impairment of glucose tolerance. It may make hyperglycemia worse in diabetic patients and it may precipitate hyperglycemia in nondiabetic subjects. The latter effect may indicate a state of latent diabetes mellitus, not otherwise detectable, and suggests a possible diagnostic role of thiazide compounds, thereby producing from an unwanted effect something possibly meaningful.

Summary and Conclusions

1. Two hour post prandial blood specimens were obtained for glucose determination before and after administration of either chlorothiazide or trichloromethiazide in twenty-five hospitalized ambulant patients after a week's stabilization of illness and unrestricted high carbohydrate diet. All but one had no knowledge of diabetes mellitus.

2. Fourteen of the twenty-five patients showed a value greater than 120 mg. per cent after thiazide administration. Of these fourteen, the control value was less than 120 mg. per cent in four and greater in ten. In these ten, all with a control value greater than 120 mg. per cent, the glucose level after thiazide administration was higher in six, unchanged in one and less in three.

3. A total of ten of the twenty-five patients had an increase in blood glucose values to abnormal levels after thiazide administration, ranging from 6 to 70 mg. per cent over control values.

4. Thiazide compounds may precipitate or intensify hyperglycemia.

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Saluretic Drugs and Diabetes Mellitus*

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THE benzothiadiazine derivatives can exacerbate the course of a previously well controlled diabetic patient and can also cause development of an overt symptomatic diabetes in a subclinical latent case.[1-7] The following case report illustrates the importance of recognizing this relationship.

ILLUSTRATIVE CASE

A seventy-eight year old retired textile importer was admitted to St. Vincent's Hospital complaining of severe substernal pain. Serial electrocardiograms showed the evolution of an acute anterior myocardial infarction. There was a corresponding febrile response with a rise in the white blood count, sedimentation rate and serum transaminase levels. Previous chest pain was denied. However, he did state that for several years he had intermittent ankle edema and at one time received digitalis. The past medical history was otherwise unremarkable. He denied diabetes and a family history was negative for diabetes.

Physical examination revealed a white man who appeared younger than his stated age. The only abnormal findings were distant heart sounds, basilar pulmonary rales, a palpable liver and one plus ankle edema. Bed scale weight was 155 pounds.

On the day following admission the fasting blood sugar was 147 mg. per cent; blood urea nitrogen, 25 mg. per cent; urinalysis showed a trace of albumin but no glucose. A fasting blood sugar on the third day was 132 mg. per cent. Urines were then tested for sugar and acetone four times a day for six days. Only one specimen showed a trace of glucose. A postprandial blood sugar on the ninth day was 224 mg. per cent. At this point he was considered to have latent diabetes and was given a 1,600 calorie diabetic low sodium diet. Periodic urines remained negative for sugar.

The hospital course was uneventful. The basilar rales, hepatomegaly and dependent edema were easily controlled with meralluride sodium. A week before discharge he was ambulated and at the same time was digitalized with digoxin and given hydrochlorothiazide 50 mg. once a day. Two days before leaving the hospital his fasting blood sugar was 74 mg. per cent. He was discharged on the 31st hospital day. At this time he weighed 150 pounds.

Subsequent Course: At home his wife elected to follow rigidly the diet prescribed in the hospital. Daily weights remained at 150 pounds, plus or minus one-half pound. He made his first office visit six weeks after discharge. Progress was considered excellent. His weight was 150 pounds. A week later he volunteered that urinary frequency was annoying. At this visit he weighed 148 pounds. On his next visit, two weeks later (ten weeks after starting hydrochlorothiazide 50 mg. daily), he complained of feeling poorly. Specifically he noted weight loss, polyuria and polydipsia. Physical examination was unremarkable except that he now weighed 143 pounds, a total weight loss of seven pounds in three weeks.

Hydrochlorothiazide exacerbation of his latent diabetes was then considered. Blood sugar at this time was 300 mg. per cent and urinalysis revealed four plus sugar and four plus acetone. The hydrochlorothiazide was immediately discontinued and within two days the acetone cleared. However, he continued to have one to two plus glycosuria and a week later had lost one more pound and his blood sugar remained at 300 mg. per cent. Because of the weight loss and the patient's own anxiety, he was given 125 mg. of chlorpropamide daily and after ten days (seventeen days after hydrochlorothiazide was discontinued), glycosuria disappeared. His blood sugar was 114 and 112 mg. per cent during the second and third week of chlorpropamide therapy. He had regained three pounds. After three weeks the chlorpropamide was stopped and since then his urine has been glucose-free. He maintains a 2,000 calorie diabetic low sodium diet and receives periodic meralluride sodium for edema control. His last fasting blood sugar was 92 mg. per cent.

Comment: This patient's subclinical diabetes was unmasked by the stress reaction accompanying a myocardial infarction. It was, however, mild and easily controlled by diet. In this case a small amount of hydrochlorothiazide, 50 mg. daily, did not provoke overt clinical diabetes until ten weeks after it was initiated. There was immediate but not complete amelio-

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ration of the condition after discontinuing the drug. Chlorpropamide was used here because of the patient's anxiety and weight loss. It was discontinued after three weeks and since then urines have been glucose-free and fasting blood sugar has been normal.

Comments

Wilkins[1] was the first to call attention to the occurrence of hyperglycemia and glycosuria in patients receiving benzothiadiazine derivatives. He raised the question of cause and effect relationship. Finnerty[2] mentioned the phenomenon in three patients using chlorothiazide. Two of these had an aggravation of pre-existent diabetes and the other was not known to have had a previous diabetic tendency. Freis[3] noticed the relationship in two of his patients who were receiving hydrochlorothiazide. Hollis[4] reported a mother and daughter with occult diabetes aggravated by chlorothiazide.

Goldner, Zarowitz and Akgun[5] reported a patient with familial history of diabetes mellitus who suddenly developed moderately severe clinical diabetes after changing from meralluride sodium to chlorothiazide. Tolbutamide caused a partial amelioration but it was not until chlorothiazide was discontinued that the blood sugar returned to normal levels. These investigators then gave large doses of the benzothiadiazine derivatives to twenty nondiabetic and twenty diabetic subjects. Serial urines for glucose, fasting blood sugars and electrolyte determinations were followed. The nondiabetic patients failed to show any rise in blood sugar or glycosuria. Pre- and postbenzothiadiazine glucose tolerance tests in four of these showed no change. On the contrary, six of the twenty diabetic patients evidenced an aggravation of their disease. The increase in blood sugar and glycosuria occurred three to five days after the start of therapy and returned to pretreatment levels as soon as the medication was discontinued. In the remaining fourteen diabetic subjects there was no adverse effect on their clinical or chemical status.

The exact physiochemical mechanism of the benzothiadiazine derivatives in intensifying the diabetic tendency is not yet established. The phenomenon can also occur in diabetic patients receiving insulin and the arylsulfonylurea drugs as well as in the nonmedicated patient with latent diabetes. That only a small minority of diabetic patients exhibit this effect is interesting.

Today with so many hypertensive and edematous patients receiving these valuable diuretic agents, the clinicians must be alert to this important side effect. Polyuria, weight loss and weakness, which are to be expected with the use of the saluretic drugs, may not always be salutary. If the patient reports such symptoms after the expected initial diuresis, a review of his diabetic history, urinalysis and fasting blood sugar are in order.

At the time of this writing, the following drugs have been incriminated as a cause of intensifying diabetes: chlorothiazide,[1,4,5] hydrochlorothiazide, hydroflumethiazide[6,7] and benzyhydroflumethiazide.[5,7]

Summary

The saluretic drugs can exacerbate the course of a previously well controlled diabetic patient and can also provoke the development of overt symptomatic diabetes in a previously latent case. A patient exhibiting the latter phenomenon is described. The clinician is advised to be alert to this untoward reaction.

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New Methods

Clinical Coronary Angiography*

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CORONARY angiography is not likely in the foreseeable future to become a routine or even a frequent diagnostic procedure. Nevertheless, technics are currently available which, without significant trauma or risk to the patient, regularly will demonstrate the coronary artery tree.[1–5]

At present, coronary arteriography is performed for any of several reasons. It is done, for the most part, in relatively young patients with progressive, refractory or disabling angina pectoris for whom surgical therapy is contemplated. Here the presence of focal or isolated disease is sometimes considered an indication for such treatment. It is used to determine the status of the coronary system in individuals with obscure chest pain and also is being done during the course of cardiac catheterization in subjects with valvular or congenital disease. In this circumstance angiography adds little in time or discomfort to the primary procedure and sometimes affords an opportunity for the study of the coronary arteries in relatively normal hearts. It also helps to evaluate the role of the coronary system in patients with aortic valve disease and angina pectoris.

The means by which coronary angiography was performed in this study is a development and extension of the method of vascular intubation originally described by Seldinger[6] and modified by Odman.[7] The procedure was redesigned specifically for use in coronary opacification by Bellman,[5] Williams et al.,[8] in this laboratory and at the Beth Israel Hospital in Boston. Without surgical exposure, it makes possible the intravascular insertion of a catheter as large as or even larger than the needle used for the puncture.

METHOD

All patients receive penicillin the evening before the procedure and are premedicated with meperidine and secobarbital. Following preparation of the right inguinal region, local anesthesia is obtained with procaine. A short bevel, thin-wall No. 14 needle with obturator is carefully introduced into the femoral artery through a 2 mm. skin incision and the stylet removed. A special flexible metal guide† is passed through the needle and, with care, up the femoral artery to the aortic bifurcation. The needle is then removed over the guide which is allowed to remain in the artery. A preformed loop-end catheter‡ is straightened out in the hand and threaded over the free end of the guide until it reaches the skin. The guide is sufficiently longer than the catheter so that it extends beyond it and can be grasped separately. The guide and the catheter together are then advanced until the catheter penetrates well into the artery. The catheter, which has approximately the same dimensions as the No. 14 needle, effectively obturates the arterial puncture and stops oozing which sometimes occurs around the

† The guide resembles a piano string and is fabricated of stainless steel wire wound around a central core of similar material. It is 125 cm. long and 0.060 inch thick. The core is joined at one end to the outer wire by a polished silver bead but is 5 cm. shorter than the winding at the other end. This leaves a soft, centerless tip also sealed with a silver bead. Such guides may be obtained from Codman and Shurtleff Co. of Boston, Massachusetts and from Cardiosonics, Belmont, Massachusetts.

‡ The catheter is of polyethylene tubing having an inner diameter of 0.070 inch and an outer diameter of 0.110 inch. It is commercially available as PE 260 from Clay-Adams Co. of New York. One end of the catheter is formed over a soft copper wire into a 2.5 cm. loop oriented at right angles to the shaft. It is immersed in boiling water for one minute and the wire removed after cooling. The catheter retains its new form at room and body temperatures. The end is slightly constricted by stretching and three small holes are drilled in the inferior surface of the loop.

* From the Veterans Administration Hospital, West Roxbury, Massachusetts.

TABLE I
Summary of Clinical Diagnoses and Angiographic Findings

Case No.	Age (yr.)	Clinical Diagnosis	Angiographic Findings
1	38	Duodenal ulcer	Normal
2	47	Rheumatic heart disease, mitral stenosis	Normal
3	39	Rheumatic heart disease, mitral stenosis	Unsatisfactory
4	38	Rheumatic heart disease, mitral stenosis	Unsatisfactory
5	35	Rheumatic heart disease, mitral regurgitation	Normal
6	62	Rheumatic heart disease, mitral stenosis	Right coronary artery occluded near origin, left normal
7	42	Rheumatic heart disease, mitral stenosis, mitral regurgitation, aortic regurgitation	Normal
8	33	Rheumatic heart disease, mitral stenosis, mitral regurgitation, aortic regurgitation	Normal
9	63	Rheumatic heart disease, aortic regurgitation	Unsatisfactory
10	31	Rheumatic heart disease, aortic stenosis	Normal
11	44	Rheumatic heart disease, aortic regurgitation	Normal
12	24	Rheumatic heart disease, mitral stenosis	Normal
13	41	Rheumatic heart disease, mitral stenosis	Normal
14	32	Rheumatic heart disease, mitral regurgitation	Tortuous left coronary artery, normal right
15	39	Rheumatic heart disease, aortic regurgitation	Normal
16	52	Arteriosclerotic heart disease, angina pectoris	Abnormal; tortuous left coronary artery with extensive branching and tortuosity; minute remnant of right coronary artery
17	36	Arteriosclerotic heart disease, angina pectoris	Small tortuous left coronary artery with multiple branching
18	65	Arteriosclerotic heart disease, angina pectoris, ventricular hypertrophy, congestive failure	Large, tortuous vessels with moth-eaten appearance
19	65	Arteriosclerotic heart disease, angina pectoris, myocardial infarction	No filling right coronary artery, left dilated, tortuous
20	40	Arteriosclerotic heart disease, myocardial infarction with ruptured papillary muscle	No filling left coronary artery, right tortuous and dilated
21	53	Arteriosclerotic heart disease, angina pectoris, positive exercise tolerance test	Localized block in left anterior descending coronary artery
22	50	Arteriosclerotic heart disease, angina pectoris, old myocardial infarction	Incomplete block right coronary artery, narrowing and irregularity left
23	57	Arteriosclerotic heart disease, angina pectoris	Unsatisfactory; tachycardia
24	53	Hypertensive, arteriosclerotic heart disease, failure	Unsatisfactory
25	51	Rheumatic heart disease, aortic stenosis and regurgitation, congestive failure, angina pectoris	Large right coronary artery, large, tortuous left, small saccular dilatation
26	31	Arteriosclerotic heart disease, angina pectoris	Small right coronary artery, tortuous left
27	45	Arteriosclerotic heart disease, positive exercise tolerance test, angina pectoris	Normal
28	42	Arteriosclerotic heart disease, angina pectoris	Small right tortuous coronary artery, moth-eaten left
29	65	Arteriosclerotic heart disease, myocardial infarction, angina pectoris; repeat of No. 19	No filling right coronary artery, tortuous dilated left
30	57	Arteriosclerotic heart disease, angina pectoris; repeat of No. 23	Unsatisfactory; tachycardia
31	49	Rheumatic heart disease, mitral stenosis, arteriosclerotic heart disease	No filling right coronary artery, tortuous left
32	66	Hypertensive, arteriosclerotic heart disease, angina pectoris	Normal right coronary artery, tortuous irregular left
33	58	Arteriosclerotic heart disease, myocardial infarction, angina pectoris	Normal right coronary artery, incompletely occluded left with branching and tortuosity
34	49	Arteriosclerotic heart disease, myocardial infarction, angina pectoris	Normal right coronary artery, left irregular with small localized dilatations
35	34	Arteriosclerotic heart disease, angina pectoris	Normal right coronary artery, localized block in left anterior descending

TABLE I
Summary of Clinical Diagnoses and Angiographic Findings (*Continued*)

Case No.	Age (yr.)	Clinical Diagnosis	Angiographic Findings
36	53	Arteriosclerotic heart disease, angina pectoris; repeat of No. 21	Normal right coronary artery, moth-eaten left with large collaterals
37	48	Arteriosclerotic heart disease, angina pectoris, myocardial infarction	No filling right coronary artery, abnormally narrowed tortuous left
38	47	Rheumatic heart disease, aortic stenosis and regurgitation, angina pectoris	Large tortuous right and left anterior descending arteries; patchy opacification of left marginal branch, circumflex not seen
39	45	Arteriosclerotic heart disease, old myocardial infarction	Normal
40	42	Carotid artery insufficiency	Unsatisfactory, tachycardia
41	34	Idiopathic cardiac hypertrophy	Normal, large vessels
42	26	Rheumatic heart disease, mitral stenosis	Normal
43	39	Rheumatic heart disease, aortic regurgitation; repeat of No. 15	Normal
44	67	Pulmonary emboli, cirrhosis	Normal
45	55	Atrial septal defect, hypertrophy	Normal
46	51	Rheumatic heart disease, aortic stenosis	Normal
47	37	Idiopathic myocardial hypertrophy	Large, otherwise normal coronary arteries
48	49	Rheumatic heart disease, mitral stenosis	Normal
49	52	Rheumatic heart disease, mitral stenosis	Normal
50	48	Rheumatic heart disease, aortic stenosis	Normal
51	38	Pericarditis	Normal
52	37	Idiopathic cardiac hypertrophy, atypical chest pain	Normal
53	51	Osteoarthritis, chest pain	Unsatisfactory
54	54	Atypical chest pain	Normal
55	31	Atypical chest pain	Normal
56	51	Atypical chest pain	Nonfilling of right coronary artery, tortuous left with filling defects
57	37	Idiopathic hypertrophy, atypical pain; repeat of No. 52	Normal
58	36	Pericarditis, atypical chest pain	Normal
59	53	Rheumatic heart disease, aortic stenosis, atypical chest pain	Right coronary artery normal, left, unusual branching and tortuosity
60	46	Atypical chest pain	Normal

metal guide. At this time the guide is withdrawn from the catheter a distance of 3 to 5 cm. and the two together advanced a like distance. This is repeated several times until only the soft leading end of the guide (5 cm. as determined earlier by measurement of the catheter against the guide) remains extended beyond the catheter. The two are then advanced under fluoroscopic guidance up the aorta and over the arch to a point where the tip of the guide appears at the approximate level of the aortic valve. The guide is then completely removed from the catheter which is separately advanced another 10 cm. to make up for its position 5 cm. back of the guide tip and for the shortening which results from reforming of the loop.*

The catheter is connected to an elevated infusion flask containing 15 mg. of heparin in 1 L. of 5 per cent glucose solution. Enough height is maintained to permit a constant slow drip. The position of the loop is checked by fluoroscopy following introduction into the catheter of 5 ml. of contrast substance, and adjustment made when indicated. A measured quantity, generally 30 ml. of the warmed contrast material,† is then injected and serial x-ray films made with appropriate radiographic equipment.‡ Slowing of the heart is obtained by bilateral carotid compression.

* The apparatus is, perhaps, more easily understood if the wire guide is pictured as a long flexible replacement for the normal needle obturator and the catheter as a long atraumatic needle put on over the guide.

† Diatrozoate methylglucamine, supplied as Cardiografin 85 per cent through the kindness of Dr. Milton N. Donin of the Squibb Foundation for Medical Research.

‡ A Fairchild camera was used capable of making one 10 by 10 inch picture every 0.6 second. A 200 ma. 100 Kv portable x-ray apparatus produced adequate P-A films at 0.1 second exposures. However, the exposure time was much too long and the films too infrequent when tachycardia could not be controlled. The penetration was inadequate for rapid lateral films.

FIG. 1. Case 1. Normal coronary angiogram in a young man without heart disease. Arrow points to the left circumflex artery which is not well shown. The other vessels on the left side are the left anterior descending artery and the left marginal branch.

Cardiac activity is monitored at all times by an oscilloscopic electrocardiograph and, though it has never been needed, equipment is at readiness for ventricular defibrillation and artificial pacemaking. At the conclusion of the procedure, the catheter is removed and pressure maintained over the puncture site for five to fifteen minutes. A sandbag is then placed over the dressing for another hour. The patient is allowed to walk the same day and is ready for release from the hospital the following morning.

MATERIAL

When this report was prepared coronary angiography had been accomplished sixty times in fifty-five patients (Table 1). All were men between the ages of twenty-four and sixty-seven years. It was done twice in three patients because of initially unsatisfactory results, in one to evaluate the results of surgery and in another to assess an improvement in symptoms. The catheter could not be advanced beyond the aortic bifurcation in several others who are not included in this report.

Nineteen of the fifty-five patients had disabling angina pectoris and were being considered for surgical treatment. Nine had chest pain of unknown cause and twenty-six patients were studied during the course of cardiac catheterization for noncoronary heart disease. Several patients having aortic stenosis with angina pectoris were studied in an effort to determine whether or not the pain was due to associated coronary disease. All subjects had complete clinical studies including routine laboratory tests and, when resting electrocardiograms were normal, exercise tolerance tests.

RESULTS

Satisfactory diagnostic roentgenograms were obtained in fifty-two of the sixty attempts (Table 1). Inadequate opacification occurred eight times in seven patients. In one patient with free aortic regurgitation (Case 9), turbulence at the root of the aorta apparently prevented adequate concentration of the opaque material. All other failures were attributed to tachycardia which could not be controlled by carotid artery compression. The best results occurred in those instances in which three to six second asystole was effected.

A few normal angiograms were obtained in patients with valvular heart disease without significant hypertrophy and in occasional subjects with chest pain later proved to be of noncoronary origin. These were used as a basis for comparison.

ABNORMAL FINDINGS

Deviations from normal included the following: (1) Nonfilling of a major vessel on repeated injections despite good opacification of the corresponding coronary sinus; (2) localized obstruction distal to the coronary ostia; (3) spotty, moth-eaten appearance of the opacified vessels, small filling defects; (4) tortuosity, twigging or branching and multiplication; (5) localized dilatations with intervening constrictions having the appearance of ectasia or aneurysm formation; (6) apparent recanalization; (7) combinations of these abnormalities and (8) enlargement of the coronary bed in ventricular hypertrophy with or without tortuosity.

There were two other apparently physiologic but totally unexpected findings of uncertain validity. The left coronary system regularly opacified before the right except in the presence of left vessel disease. One patient in four without the clinical findings of aortic incompetence exhibited contrast substance in the left ventricle implying aortic valve regurgitation.

Filling Defects: The normal coronary tree is rather simple, with small, relatively straight vessels and a few visible branchings (Fig. 1). Of the abnormalities, total nonfilling of a major

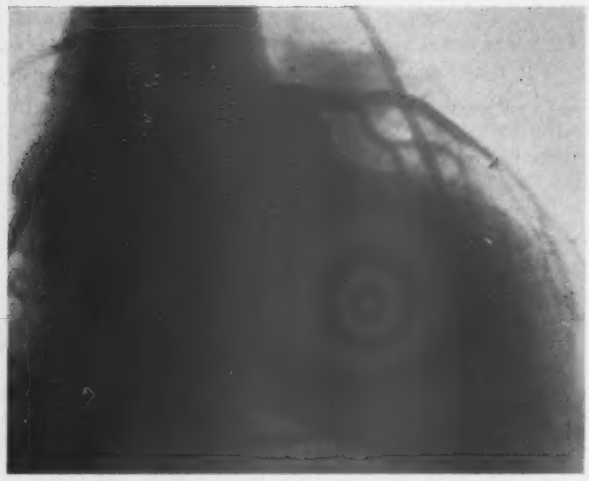
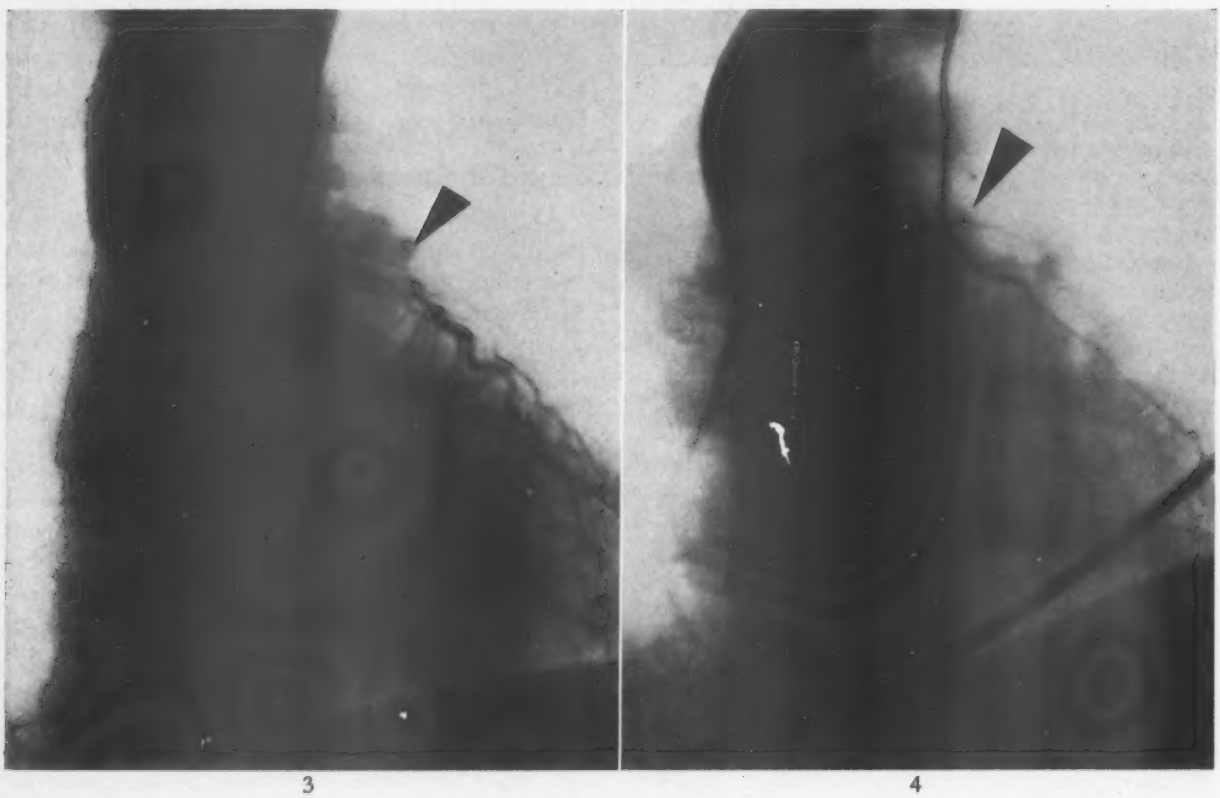


FIG. 2. Case 12. A twenty-four year old white man with mitral valve disease. The loop of the catheter is in the left ventricle which is well opacified. Note the excellent filling of the left coronary artery. The right coronary artery does not fill. It did opacify, however, several frames later.

trunk (always the right) has been the most unsatisfactory and difficult to assess single finding (Fig. 2). We suspect that this lack of opacification often may be technical rather than organic and have not accepted this as evidence of coronary disease unless the vessel failed to appear on repeated injections despite good filling of the corresponding coronary sinus. In any event, it was not accepted as indubitable evidence of disease in the absence of associated abnormalities of the visible vessels. These were generally large (very rarely small), tortuous and exhibited many branches and twigs, sometimes to an extraordinary degree (Fig. 3). Obstructions beyond the ostia appeared on successive injections and generally were complete (Figs. 4 and 9). In some instances, however, persistent remnants of varying dimensions could be seen (Figs. 5 and 6).

Localized Narrowing and Dilatation, Filling



3 4

FIG. 3. Case 33. A fifty-eight year old man with disabling angina pectoris. Arrow points to an area of local narrowing. The left anterior descending artery is well filled beyond this, but is very tortuous and exhibits numerous small vessels emanating from it. There is a curious stirrup-shaped vessel leaving the main left coronary artery which may be a remnant of the circumflex artery. The right coronary artery is not well seen in this roentgenogram, but was well visualized several frames later. Note contrast material in the left ventricle. The obstruction was confirmed at operation but could not be resected. A fibrous cord was all that remained of the left circumflex artery.

FIG. 4. Case 35. A thirty-four year old man with increasing angina pectoris. The arrow points to the occluded left anterior descending artery. This was confirmed at operation and endarterectomy was performed.

FIG. 5. Case 17. A thirty-six year old man with severe angina pectoris on effort. The large arrow points to what is believed to be an incomplete occlusion of the main left coronary artery. There is a tiny remnant of the left circumflex (small arrow) and several small channels representing channels or recanalization of the left anterior descending and marginal branches. There is a huge right coronary artery with extensive and tortuous branchings reaching to the apex.

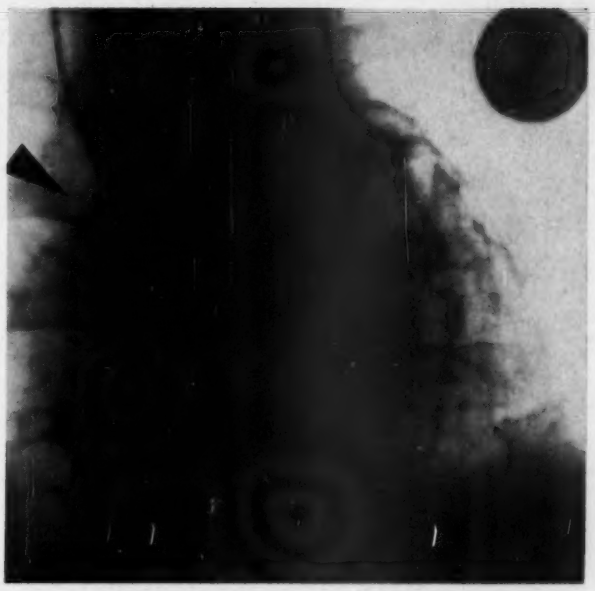


FIG. 6. Case 16. A fifty-two year old man with severe angina pectoris. The arrow points to a minute figure-of-eight remnant of the right coronary artery. The main left artery and all its branches are large and tortuous.

Defects: Still other abnormalities resembled those seen in peripheral arterial disease elsewhere in the body. They included the patchy, moth-eaten appearance of sclerotic, partially occluded arteries (Fig. 7). Localized narrowing and filling defects were seen, generally in the left coronary artery and characteristically just proximal to or at the orifice of the circumflex artery (Fig. 3). Several studies showed spherical areas separated by narrower bands having the appearance of localized dilatations (Fig. 8A). One saccular dilatation also was seen (Fig. 8B). In cardiac hypertrophy the vascular bed was large and tortuous (Fig. 9).

Recanalization and Collateral Vessels: Examples were noted of what almost certainly was recanalization of occluded vessels or the development of collaterals. Occasionally, many minute arteries could be seen emanating from such diseased vessels. One patient on whom serial studies were performed showed the presence of such channels arising from an occluded area in the left anterior descending coronary artery where none was present seven months earlier (Fig. 10).

Asynchronous Coronary Filling and Aortic Regurgitation: The observation of asynchronous coronary filling (Fig. 2) and apparent aortic regurgitation (Figs. 3, 7 and 10) may be factitious and related somehow to the technic. There is no physiologic reason known to us why the left coronary artery should fill before the right and no theory is offered in explanation. Aortic incompetence, however, may well be present normally in that period of systole just prior to valve closure and would not, therefore, produce a murmur in diastole. Accordingly, when contrast substance is administered, a small quantity would appear in the ventricle. This phenomenon was not encountered more often in patients with nonaortic valvular disease than in those without any valvular abnormalities. The method used was not sufficiently precise to determine the exact moment of regurgitation within the cardiac cycle.

CORRELATION OF ARTERIOGRAMS AND CLINICAL FINDINGS

When, over a thirteen month period, sixty studies had been made, the collected but unidentified arteriograms were separately considered and the interpretations compared with

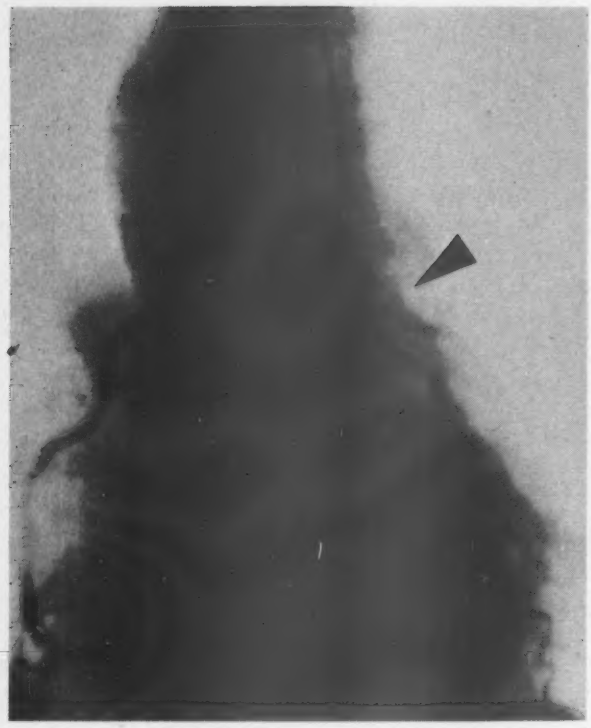


FIG. 7. Case 38. A forty-seven year old man with aortic stenosis and insufficiency and with disabling angina pectoris. The arrow points to patchy opacification of the left marginal branch which terminates in a filamentous channel. The circumflex vessel cannot be identified. The right coronary and the left anterior descending arteries are large and tortuous.

the known clinical patterns. It was impossible to be unaware completely of the identity of some of the cases since certain distinctive findings could be recalled. In these instances, however, interpretation was made solely according to the already established criteria, mentioned previously, and as objectively as possible.

Except for two patients with apparently normal angiograms (Cases 27 and 39), significant abnormalities were seen in all patients with clinical coronary heart disease. Almost all subjects with valvular or congenital defects and those whose chest pain was due to noncardiac causes exhibited normal vascular patterns. Three relatively elderly patients without symptoms of coronary disease showed vascular abnormalities. No correlation was apparent in this limited study between the type of coronary abnormality and the character of the symptoms.

Normal Arteriogram in Clinical Coronary Disease: The two patients with clinical coronary disease and apparently normal coronary arteriograms deserve separate consideration. One is a patient with angina pectoris and a positive exercise tolerance test (Case 27). The symptom is of one year duration and there has been no clinical episode suggesting an acute occlusion

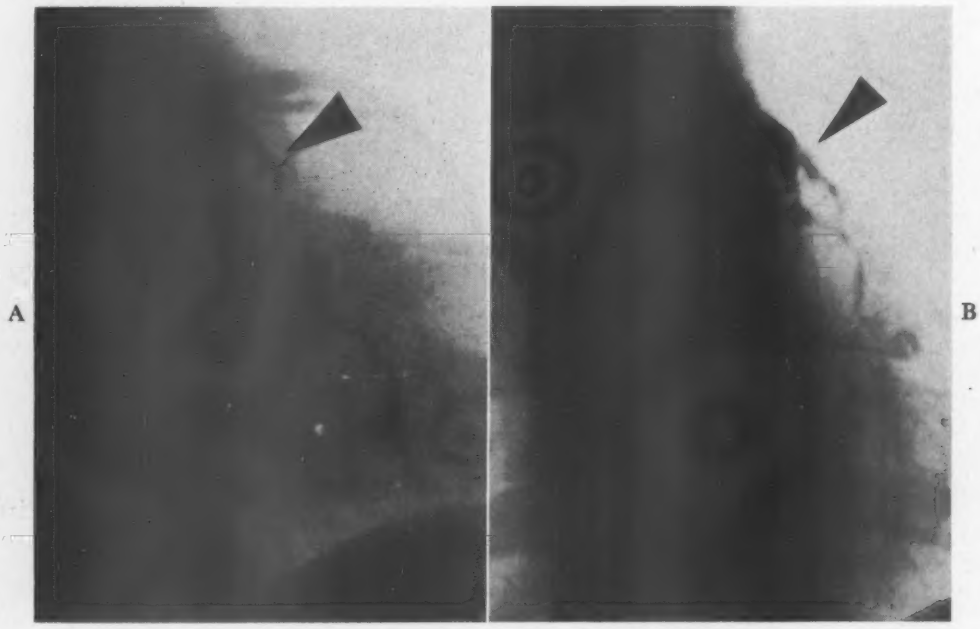


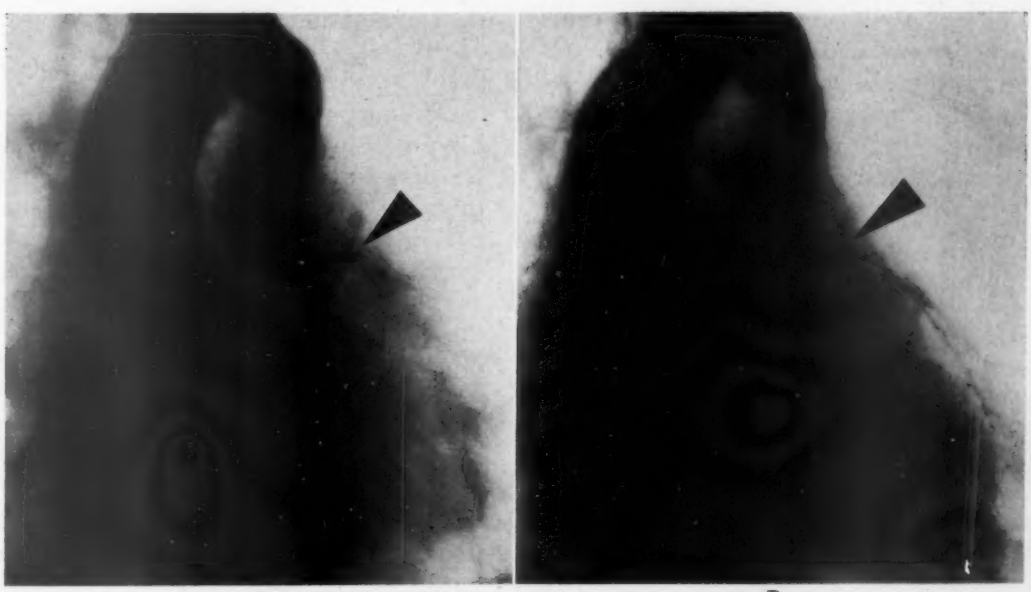
FIG. 8. Dilatations of coronary vessels. A, Case 25. A fifty-one year old man with aortic stenosis and angina pectoris. Arrow points to a saccular dilatation of the left circumflex artery shortly beyond its origin. B, Case 34. A forty-nine year old man with disabling angina pectoris. Arrow points to fusiform dilatations of the main left coronary artery and its unidentified branches. Threadlike vessels are visible distal to the dilated area.

or myocardial infarction. The second patient (Case 39) is forty-five years old and experienced an unequivocal myocardial infarction sixteen months earlier. However, he has no angina pectoris at this time and a negative exercise tolerance test.

It is possible in these patients that better technic might have demonstrated small vessel disease which was not apparent by the method employed. If true, however, this would have been in total contrast to the other patients in whom large vessel disease was the rule. It appears most unlikely that complete, smooth recanalization could have occurred together with restoration of normal appearance. Moreover, it must be noted that the first of these patients still experiences angina pectoris. This discussion cannot further be continued in the light of our limited present knowledge but must await a wider experience with coronary examination in live subjects.

Surgical Correlations: Seven patients in this series (Cases 20, 23, 26, 28, 29, 33 and 35) were operated upon (by Dr. Richard Warren), one (Case 20) for repair of a ruptured papillary muscle and the others for relief of angina pectoris. In the six instances in which adequate films were obtained, the preoperative angio-

FIG. 9. Case 18. A sixty-five year old man with aortic pseudostenosis, gross cardiac hypertrophy, angina pectoris and congestive failure. Note large tortuous channels without apparent obstructive changes.



A B

FIG. 10. Development of collateral vessels. A, Case 21. A fifty-two year old man with severe angina pectoris. Arrow points to localized obstruction of the left anterior descending artery. B, Same patient seven months later (Case 36). Note large channels (arrow) emanating from the point of obstruction. Patient clinically was much improved. Note also opacification of the left ventricle.

graphic diagnosis was confirmed entirely (Figs. 3 and 4). Endarterectomy was performed in two patients in whom this was possible, phenolization and poudrage in the others. The patient in Case 20 did not survive the procedure and another (Case 33) died of an acute myocardial infarction eight months after operation. In both instances the autopsy findings agreed with the coronary angiograms.

MORBIDITY

Coronary angiography was without mortality in the sixty procedures described in this study. There were no important reactions to the contrast substance. Most patients experienced a characteristic descending flush or sensation of heat. Six subjects had nausea and three of these vomited. None had an anaphylactic reaction. No patient experienced angina pectoris during the procedure though electrocardiographic changes involving the S-T segment and the T wave were seen occasionally. A nonfatal myocardial infarction did, however, occur at another hospital in which a modification of this technic was employed. It is believed that a clot formed near the end of the catheter and was washed into a coronary artery with the injection. This patient is not included in the present report.

Local Vascular Complications: Morbidity did occur as a consequence of the large needle puncture and passage of the wire guide. Perivascular hematomas formed in six patients and once (early in our experience) a large retroperitoneal hemorrhage occurred which required surgical intervention. This almost certainly was due to injudicious passage of the wire guide which, soft though it was, penetrated the aorta at a sclerotic plaque, and to an excess of heparin (50 mg.) in the arterial drip. Nothing remotely like this has occurred in the last fifty patients. On two occasions knots formed in catheters with overlong loops and required surgical exposure of the vessel before they could be removed. Occasionally, passage of the catheter beyond the aortic bifurcation was impossible in patients with sclerotic and tortuous vessels. Two such patients subsequently experienced thrombosis of the femoral artery. In neither instance, however, was surgical intervention necessary.

COMMENT

A diagnostic procedure to be useful, must yield important information not easily attained by simpler means, have little or no patient morbidity and should not be difficult to perform. Coronary arteriography, as done in this study, fulfills most of these requirements. The method described is not difficult and is quickly accomplished with a minimum of exposure to radiant energy.* It is likely that better results will follow the use of more precise injection devices, more powerful x-ray equipment and faster cameras than were used in this study. Cinefluorography can be expected to contribute more information regarding coronary dynamics. However, fine anatomic details are less well shown by this method. The morbidity is not prohibitive and should diminish, as it has in our hands, with increasing experience.

Coronary angiography appears, at present, to be most useful in determining the presence of localized, possibly resectable, disease in the major coronary branches. It seems unlikely, at this time, that coronary artery surgery is feasible in aged patients and in those with multiple infarctions or other evidence of extensive disease. Accordingly, arteriography has not been done in such cases and no studies are available for comparison. Except for this group, the results obtained in patients with clinical coronary insufficiency suggest that it is almost always the result of vascular changes of a type and degree which can be demonstrated by angiography. Coronary arteriography has also been of value in determining the cause of obscure chest pain.

SUMMARY AND CONCLUSIONS

Coronary angiography, though still an exacting procedure requiring complicated and cumbersome apparatus, has attained the stature of a practical examination. It is a relatively innocuous and atraumatic test. It is now done to help select patients for surgical treatment of angina pectoris and occasionally to determine the presence of arteriosclerotic heart disease in patients with chest pain of uncertain origin.

Enough examinations have been performed so that presumably normal coronary patterns can be recognized and used as a basis for comparison.

Abnormalities include total vascular obstructions, patchy opacification, filling defects, tortuosity and multiplication with, rarely, aneurysmal dilatations of diseased vessels.

Unexpected and possibly factitious observations suggest that the left coronary artery fills

* Fluoroscopy time is brief, rarely lasts more than two minutes and often is complete in one-half to one minute.

before the right and that one individual in four has nonclinical incompetence of the aortic valve.

Excellent angiographic correlation with the clinical pattern was noted both in the presence and in the absence of clinical coronary heart disease. Two patients, however, with clinical arteriosclerotic heart disease exhibited apparently normal coronary arteries. One patient showed unmistakable evidence of recanalization of an obstructed vessel or growth of large collaterals where none was present seven months earlier.

Angiographic diagnoses have, thus far, been confirmed in six patients who came to surgical exploration.

Acknowledgment

The authors are grateful to Dr. Boris Bushueff, roentgenologist, and the members of his department for assistance and advice in the preparation of the coronary angiograms.

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A Modification of the Technic of Transseptal Left Heart Catheterization*

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THE INTRODUCTION OF the Ross-Braunwald technic for left heart catheterization represented a major advance in achieving safe access to the left side of the heart.[1,2] Their method as originally proposed consisted of isolation of a superficial saphenous vein, passage of a No. 9 aortographic catheter to the right atrium and insertion therein of a No. 17 hollow needle with a specially curved tip, 1 cm. longer than the catheter. The catheter tip was engaged on the inferior medial wall of the atrial septum, the region of the fossa ovalis, and the needle advanced sharply at a pre-set negative 45 degree angle to a horizontal plane. A polyethylene catheter was threaded through this and the left ventricle catheterized blindly.

Modification of Technic: Subsequent to the inadvertent passage of the original No. 9 catheter through the valve of a foramen ovale, experience has accumulated utilizing deliberate introduction of the No. 9 catheter into the left atrium. To accomplish this, firm pressure is maintained on the catheter-needle junction and the two pushed forward in the original plane. A "give" is felt which indicates that the catheter has penetrated the wall and is free in the left atrium. This maneuver has been performed successfully in fifteen patients without incident or evidence of left to right shunt. After the catheter is in the left atrium the needle may be withdrawn. The No. 9 catheter may now explore the left atrium and left ventricle or a No. 5 catheter can be threaded through the No. 9 and exploration carried out. Recently, Brockenbrough and Braunwald[3] reported a similar modification, but employing a specially tapered catheter tip to facilitate transseptal passage.

Advantages of Method: The major advantages to this maneuver are the following:

1. The removal of the unyielding, sharp pointed needle. This has the advantage of safety and freedom of movement by the patient. Standard leg exercise can be performed now, the flexible catheter being led off to one side and the thigh readily flexed.
2. Controlled fluoroscopic exploration of the left atrium. This has permitted cannulation of the pulmonary veins and more ready passage through the mitral valve into the left ventricle. The larger, somewhat stiffer catheter has a major advantage over the polyethylene catheter in not being so easily deflected by large regurgitant jets.
3. Left atrial angiography can be successfully performed through the large aortographic catheter.

SUMMARY

A minor but important addition to the Ross-Braunwald technic of transseptal left heart catheterization is the passage of the initial large catheter over the puncturing needle directly into the left atrium. There appear to be no hazards and certain distinct advantages to this maneuver.

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* From the Medical Clinics, Peter Bent Brigham Hospital, and Harvard Medical School. This work was supported by grants from the United States Public Health Service (H-637) and the Massachusetts Heart Association (No. 390).

Clinical Case Conference

A Case of Congenital Heart Disease

PROCEEDINGS of weekly Case Conference, conducted by Benjamin M. Gasul, M.D., Director, and edited by Bessie L. Lendrum, M.D., Associate Director, of the Pediatric Cardiophysiology Department, Cook County Children's Hospital and Hektoen Institute for Medical Research, Chicago, Illinois. Only physicians, including the moderator, who have not seen any of the diagnostic work-up participated in the Conference.

HISTORY AND PHYSICAL EXAMINATION

Resident: This Negro child, three years and two months of age, has been followed in our cardiac clinic since the age of four months because of a murmur detected at birth. He was admitted to Cook County Hospital for cardiac investigation in July, 1960. His mother states that he has been asymptomatic except for frequent respiratory infections and possible shortness of breath on exertion. His development was normal. His present blood pressure is 104/64 in the upper and 138/78 mm. Hg in the lower extremities. His hemoglobin is 11.5 gm. per cent and the urinalysis is negative.

The following are the diagnoses made by the house staff and attending physicians, together with the physical findings upon which these diagnoses were based:

1. *Isolated pulmonary stenosis* (first year fellow): Slightly enlarged heart; thrill and grade 5 (scale 1–6) ejection murmur in the second and third left intercostal spaces parasternally; single or closely split second heart sound.
2. *Ventricular septal defect with pulmonary hypertension* (second year fellow): Pansystolic grade 5 murmur heard along the left sternal border; second heart sound accentuated, possibly narrowly split; heart active and markedly enlarged.
3. *Subaortic stenosis or interatrial septal defect* (first year fellow): Thrill in first intercostal space parasternally; grade 4–5 pansystolic murmur in second intercostal space parasternally; second heart sound decreased in intensity and narrowly split.
4. *Coarctation of the pulmonary artery branches* (first year fellow): Enlarged heart; diffuse thrill in pulmonic, aortic and infraclavicular regions; second heart sound normally split with accentuation of the second component.
5. *Ventricular septal defect complicated by a patent ductus arteriosus* (second year fellow): Thrill and grade 4 pansystolic murmur at lower left sternal border; a thrill and grade 5 pansystolic murmur in left sternoclavicular area radiating to the neck; normal second heart sound which is closely split.
6. *Acyanotic tetralogy of Fallot* (second year fellow): Enlarged left ventricle; thrill and pansystolic murmur at apex; ejection systolic murmur in the pulmonary area.
7. *Acyanotic tetralogy of Fallot* (attending cardiologist): Mild parasternal lift together with forceful apical impulse suggesting right and left ventricular enlargement; thrill well felt parasternally in second and also fourth intercostal spaces parasternally; pansystolic murmur at left lower sternal edge and apex assuming an ejection character in the pulmonary area; second heart sound probably split with a soft pulmonic closure.

Dr. Gasul: We have heard various diagnoses on this patient, including acyanotic tetralogy of Fallot, isolated pulmonic stenosis, ventricular septal defect, atrial septal defect, aortic stenosis, coarctation of the pulmonary arteries and the possibility of a patent ductus arteriosus. This Negro child does not appear to be cyanotic. We all know, however, that even a white child may have 70 to 75 per cent arterial oxygen saturation and at times still not show definite cyanosis, particularly in the presence of anemia. Let us assume the arterial oxygen saturation is normal. The cardiac apex is, it seems to me, in the fifth interspace just to the left of the

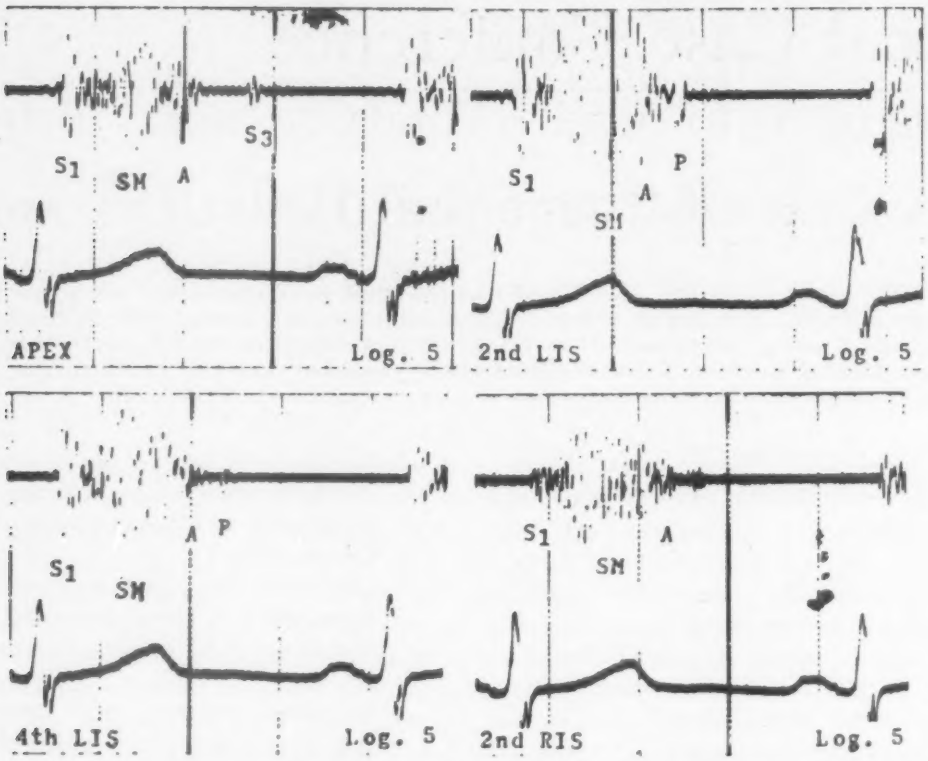


FIG. 1. *Phonocardiogram.* Note the wide splitting of the second sound, the accentuated pulmonic closure (P) and the diamond-shaped systolic murmur (SM) which starts shortly after the first sound (S_1) and extends through the aortic closure (A).

midclavicular line. I do not think there is marked cardiac enlargement; but since I feel a mild lower parasternal lift, there appears to be some right ventricular enlargement. I am very much impressed with the systolic thrill. It is most prominent over the first and second left interspaces but I can also feel it to a lesser extent over the third and fourth. The second sound in the pulmonary area is accentuated and very closely split or single. The systolic murmur is very loud, grade 4–5 in the same area as the thrill. These findings strongly suggest pulmonic stenosis and the diagnosis, it seems to me, lies between acyanotic tetralogy of Fallot and isolated pulmonic valvular stenosis. Against an isolated pulmonic valvular stenosis is the fact that I cannot hear the closure of the pulmonic valve which should be heard faintly even in severe stenosis. If the second sound is single, it would speak more strongly for tetralogy of Fallot. It is most important to make sure whether the pulmonic closure is present and faint or whether the second sound is single. The phonocardiogram is very helpful in determining this. I find no evidence of a patent ductus arteriosus since the murmur is entirely systolic, has no diastolic component and there is no evidence of marked pulmonary hypertension. Atrial septal defect alone would not cause a thrill and such a loud murmur and would have a widely split and fixed S_2. The location of the murmur and the thrill are not those of aortic stenosis. Isolated coarctation of a peripheral branch of the pulmonary artery is unlikely because the heart is enlarged and the patient is symptomatic. It is possible that after looking at the x-ray films and electrocardiogram we shall be able to say more about the diagnosis.

Question: Which chamber would you say is enlarged?

Dr. Gasul: I would say the right ventricle since the child has a lower parasternal lift.

Question: May I ask what you thought about the second component of the second sound; did you believe that if it is split, the second component is loud?

Dr. Gasul: No, I believe that the second sound is loud and either closely split or single; in other words, it is my impression that we are listening to the aortic closure here. If this is so, this would be a case of tetralogy of Fallot in which the second sound is usually single; but there are some cases of tetralogy of Fallot, particularly of the acyanotic type, in which the

delayed closure of the pulmonic valve may be heard or, if not heard, recorded on the phonocardiogram. It is my opinion that this patient has pulmonic stenosis, but whether he has a ventricular septal defect with it, I am not sure. The combination of pulmonic stenosis and ventricular septal defect is considered an acyanotic form of tetralogy of Fallot although there is a difference of opinion. Some authorities maintain that this combination should not necessarily be considered a case of tetralogy of Fallot if there is no arterial oxygen unsaturation.

Question: Could this be an atrial septal defect and pulmonic stenosis?

Dr. Gasul: If it is, I do not see how one can make the diagnosis on physical examination alone. An ejection systolic murmur is found in both lesions; that found in atrial septal defect is soft and rarely louder than grade 3; therefore, the harsh loud murmur of pulmonic stenosis would mask it. If pulmonary stenosis is severe, there may be a sizeable right to left shunt at the atrial level, the patient will then be cyanotic and the x-ray film will show diminished pulmonary vascular markings. If the shunt is left to right, however, the patient will not be cyanotic and one would expect increased pulmonary vascular markings on the x-ray film of the chest. A split second sound is present in both lesions; the splitting is usually wide and fixed in atrial septal defect. In moderate or severe pulmonic stenosis the splitting is even wider but the pulmonic component is faint or rarely, in extreme cases, not even audible. In mild stenosis the pulmonic component may be normal or loud but not fixed. Incomplete right bundle branch block is characteristic of an atrial septal defect but is also frequently found in mild or moderate pulmonary stenosis. Thus, on clinical grounds, it is often impossible to detect an atrial septal defect in the presence of pulmonic stenosis.

Phonocardiogram

Dr. Gasul: The phonocardiogram (Fig. 1) shows at the apex a systolic murmur which does not appear to be a typical holosystolic murmur even though it lasts throughout most of systole, because it has a diamond shape, starts after the first heart sound and ends at the second sound. Also recorded at the apex is a consistently seen fairly loud third heart sound occurring about 0.13 second after the second aortic sound. This is of greater intensity than the usual S_3 often recorded in children. Over the fourth left interspace parasternally, the murmur is of greater intensity than at the apex, but of the same characteristics. The murmur is even more intense in the pulmonic area and may be described there, too, as having a classical ejection or diamond shape and lasting through most of systole. A second sound of good intensity is seen immediately after the murmur ends. The murmur is distinctly less intense in the aortic area. The two components of S_2 are not evident in the pulmonary area. Whether the S_2 on the phonocardiogram recorded in the pulmonary area represents the aortic or pulmonic valve closure is not at once apparent. If it represents the aortic closure, we must conclude that the pulmonic closure is faint and may not be recorded, as in tetralogy of Fallot or severe pulmonic stenosis. On the other hand, the aortic closure sound, which normally occurs before the pulmonic closure, may be incorporated into the murmur; then the recorded S_2 represents the pulmonic valve closure. To identify the aortic component, we first identify it at the apex and time it with respect to the QRS of the simultaneously recorded electrocardiogram. Using the Q-S_2 interval thus obtained to identify the aortic closure time, we can decide whether the S_2 recorded in the pulmonic area represents aortic or pulmonic closure.

Question: Is the pulmonic closure ever recorded at the apex and could it therefore be confused with the aortic closure?

Dr. Gasul: Normally, the pulmonic closure is not heard at the apex. If pulmonary hypertension is present and the pulmonic closure is abnormally loud, it may be recorded at the apex; or if the right ventricle is grossly dilated and forms the apex, the pulmonic sound may be heard there. In this patient, timing the sounds in the manner outlined identifies S_2 in the pulmonic area as due to the pulmonic valve closure, and the aortic closure is buried within the murmur. Thus measured, the second heart sound appears to be widely split, up to 0.08 second, varying with respiration and, what is more surprising, the pulmonic closure is not of diminished intensity as would be expected in all but the mildest instances of pulmonic valvular stenosis. The intensity of this sound suggests that the pulmonary arterial blood pressure is normal or even above normal, which is a most unusual finding in both pulmonic valvular stenosis or in tetralogy of Fallot.

FIG. 2A. *Chest roentgenogram.* Posteroanterior view showing increased transverse diameter of the heart and increased pulmonary vascular markings.

CHEST ROENTGENOGRAMS

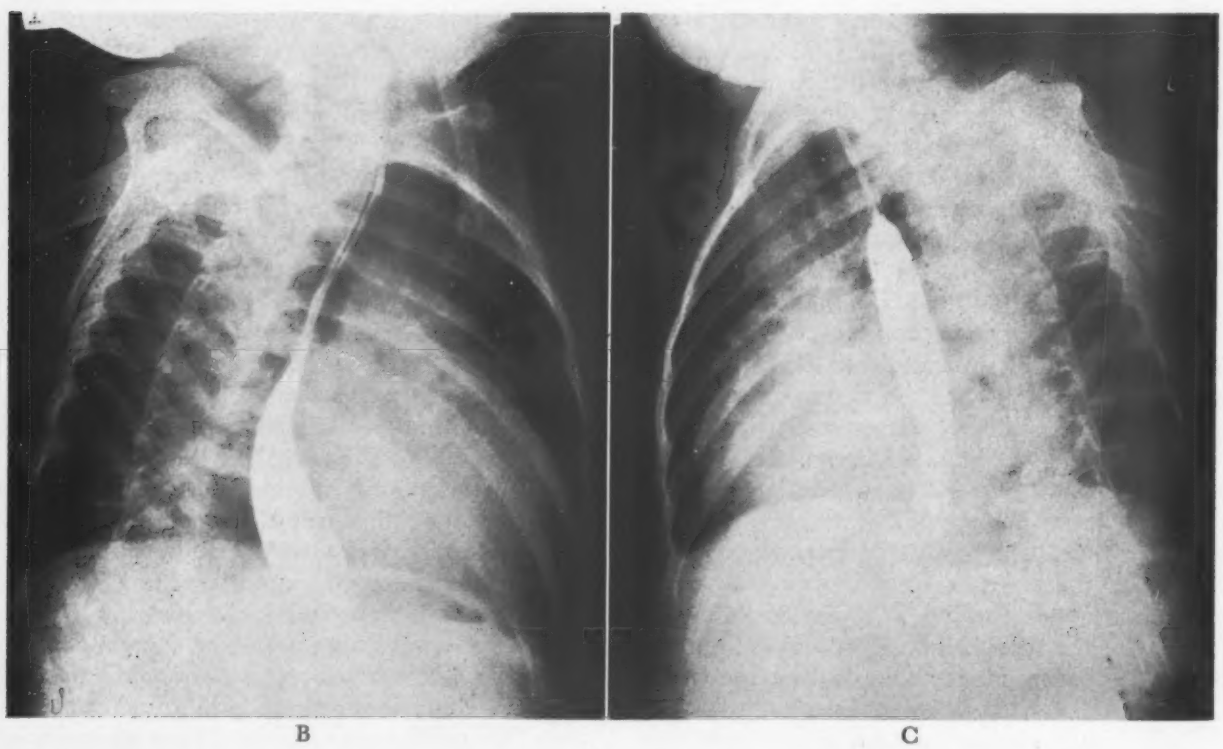
Dr. Gasul: Let us see what the x-ray films show (Fig. 2). The heart is enlarged. There is definite evidence of right ventricular and left atrial enlargement, and probably left ventricular enlargement as well. The pulmonary vascular markings appear to be increased and not diminished. These findings are compatible with a left to right shunt at the ventricular level and would exclude the presence of severe pulmonic valvular stenosis as an isolated lesion. These x-ray findings can, however, be explained by the combined lesions of ventricular septal defect with left to right shunt and pulmonic stenosis.

First year fellow: The vascular markings, to me, appear normal to diminished.

Dr. Gasul: I know how difficult it is, at times, to be certain from conventional x-ray films whether the vascular blood flow is normal, diminished or increased, and we have often been wrong in predicting pulmonary blood flows from x-ray examination. Still, to me, these appear definitely increased.

ELECTROCARDIOGRAM

Dr. Gasul: The electrocardiogram (Fig. 3) at four months of age shows an axis deviation of plus 60° and a vertical electrical position of the heart. The R wave in aVF measures 24 mm. in height which, together with the axis at this age, suggests left ventricular hypertrophy. The



B C

FIG. 2B and C. *Chest roentgenograms.* B, right anterior oblique view demonstrating posterior displacement of the esophagus. C, left anterior oblique view showing increased convexity of the anterior cardiac border and failure of the posterior border to clear the spine.

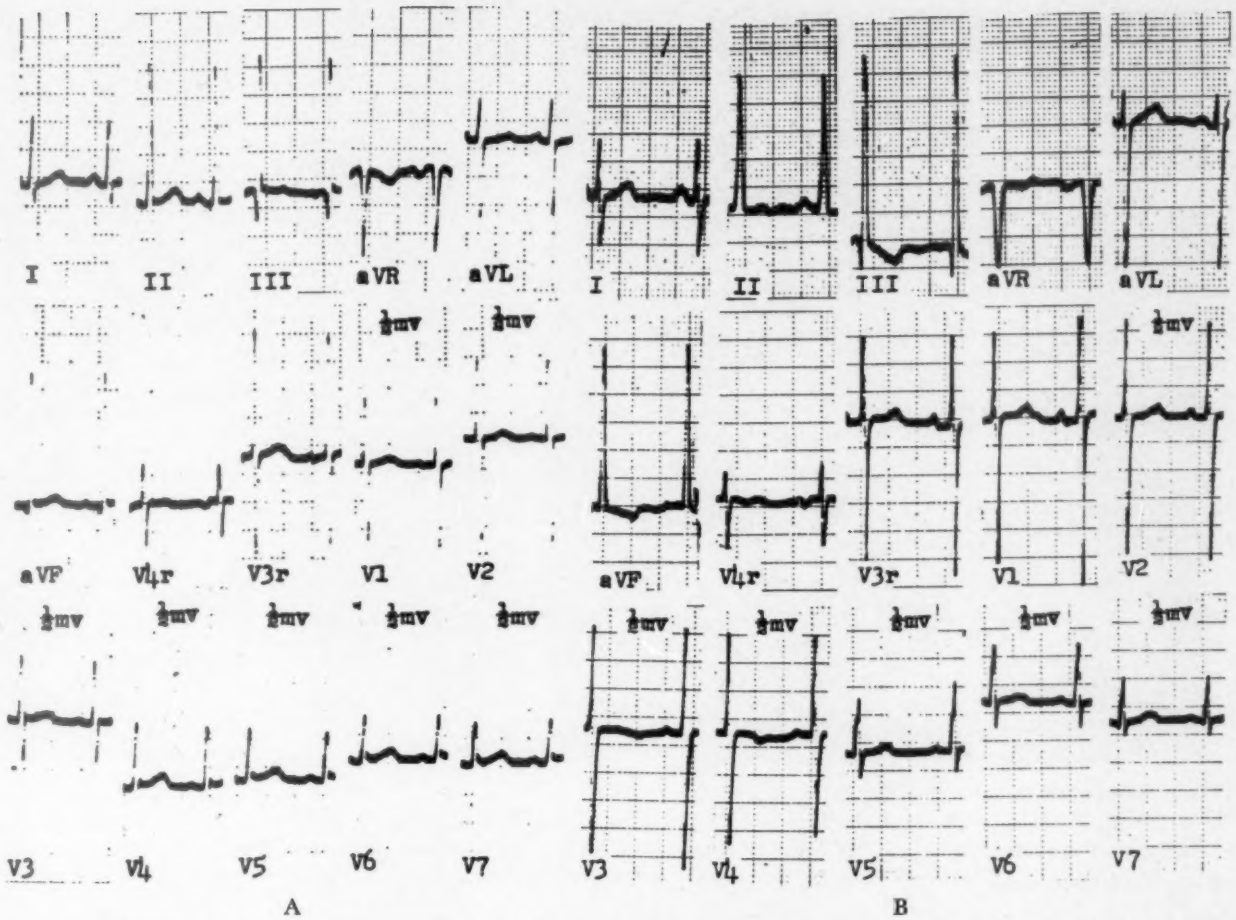


FIG. 3. *Electrocardiograms.* A, tracing at four months shows frontal QRS axis of +60°, qR complexes in V_4 through V_7 and upright T waves in the right precordial leads. B, tracing at three years shows frontal QRS axis of +90°, tall QRS complexes in leads III and aVF, RS pattern in the left precordial leads and upright T in the right precordial leads.

upward T waves in V_1 and V_3R, however, in the absence of inverted T waves in the left precordial leads, are definite evidences of right ventricular hypertrophy even in the absence of tall R waves in the right and prominent S waves in the left precordial leads. At three years of age, however, the electrical axis is plus 90° and the R wave in leads aVF, II and III are tall, measuring 27, 24 and 33 mm., respectively, denoting left ventricular hypertrophy. The T waves in V_3R and V_1 are still upright, denoting right ventricular hypertrophy. Thus, the electrocardiogram presents evidence of biventricular hypertrophy. I think we must consider the diagnosis of pulmonic valvular stenosis along with ventricular septal defect, that is, acyanotic tetralogy of Fallot, as more likely than isolated pulmonic valvular stenosis. If there is no further discussion, may we have the cardiac catheterization findings.

CATHETERIZATION FINDINGS

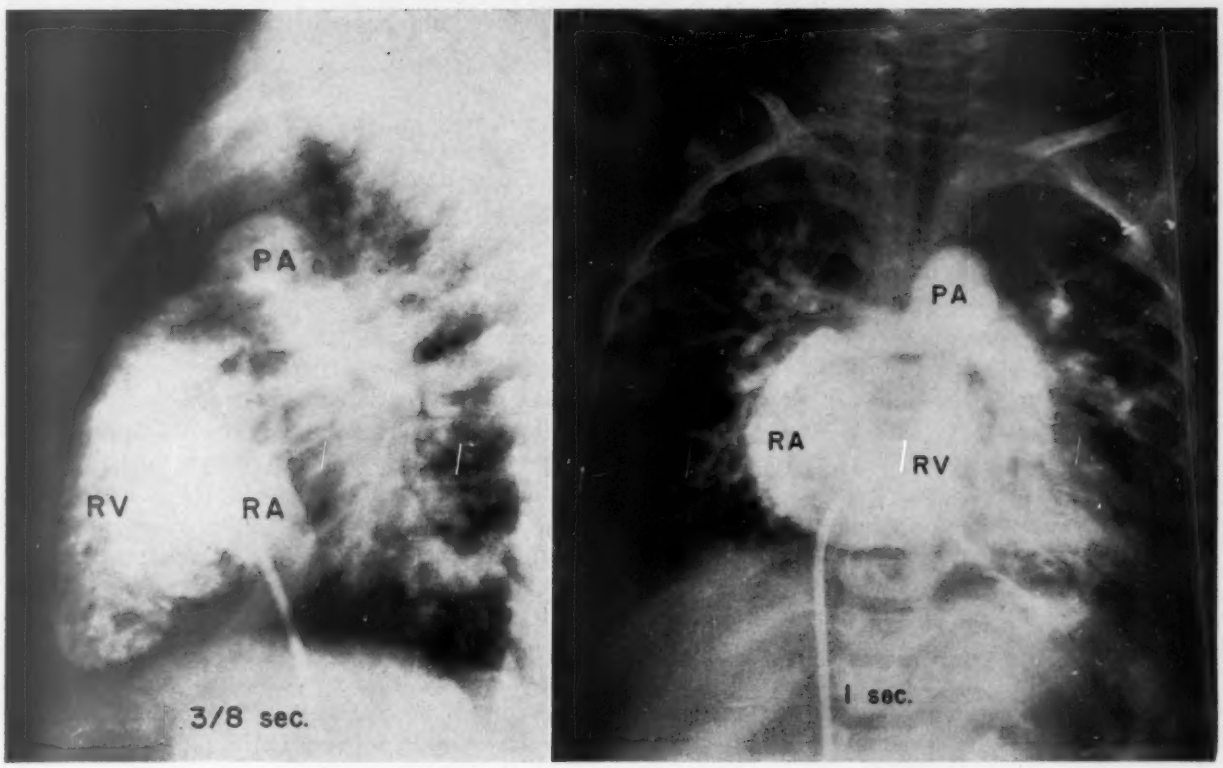
Resident: The catheter entered no unusual sites. The blood oxygen content of the superior vena cava, right atrium and right ventricle do not vary significantly (Table I). There is, however, a significant rise in blood oxygen saturation in the main pulmonary artery and both branches. Thus, there is a left to right shunt at the pulmonary arterial level due to a patent ductus arteriosus, or at a high ventricular level due to a ventricular septal defect. Not infrequently, in high ventricular septal defects streamline flow results in no detectable increase in the right ventricular blood oxygen. The systemic arterial samples (aorta) were 90 per cent saturated. This could represent a right to left shunt or could be due to mild respiratory depression and hypoxia caused by the sedation used during catheterization. The right ventricular systolic pressure was at the

TABLE I
Cardiac Catheterization Data

Catheter Site	Blood Oxygen Saturation (%)	Pressures (mm. Hg)		
		Systolic	Diastolic	Mean
Inferior vena cava	75 75 75	...	...	...
Supervior vena cava high low low	 65.5 65.5 65.5	...	...	...
Right atrium high mid low	 65.2 66.5, 65.2 66.5	...	...	3
Right ventricle outflow mid inflow	61, 61 65.5 65.5 68.5	 100 120	 0–6 0–6	...
Main pulmonary artery	77 77	45	10	24
Right pulmonary artery	75 75	...	...	...
Left pulmonary artery	77	45	10	...
Right pulmonary artery wedge	...	...	...	8.5
Aorta	89 90	110 120	50 55	80

systemic level, and a systolic pressure gradient across the pulmonic valve of at least 65 mm. Hg is found, establishing the presence of pulmonic stenosis. Surprisingly, there is an elevated pressure in the pulmonary artery where the systolic level was 45 mm. Hg. In conclusion, cardiac catheterization establishes the presence of pulmonic stenosis and either ventricular septal defect or patent ductus arteriosus with a significant left to right shunt. A small right to left shunt cannot be ruled out.

Dr. Gasul: These catheterization data confirm the clinical impression that pulmonic stenosis is present. They also explain the surprisingly loud S_2 (pulmonic closure) recorded in the pulmonary region on the phonocardiogram, since the pulmonary arterial pressure is higher than normal. The increased pulmonary vascular markings on the x-ray film are also explained by the presence of the left to right shunt. The rise in oxygen content of the blood at the pulmonary arterial level must be due to a ventricular septal defect and not to patent ductus arteriosus inasmuch as the usual continuous murmur of patent ductus arteriosus is not present, a murmur we expect to hear as long as the pressure in the pulmonary artery is not markedly elevated. This demonstrates that at least in this instance the auscultatory findings are more important in establishing the site of a left to right shunt than is cardiac catheterization.



A B

FIG. 4. *Angiocardiograms.* Contrast substance injected into the right atrium (RA). A, lateral view. Note dilated right ventricle (RV), pulmonary valvular stenosis (arrow), and poststenotic dilatation of the pulmonary trunk (PA). B, posteroanterior view. Note absence of early opacification of the aorta. The pulmonary trunk (PA) is dilated.

ANGIOCARDIOGRAPHY

Resident: Selective angiocardiography with dye injection into the right atrium (Fig. 4) shows no evidence of early opacification of the aorta, which is not visualized until the dye has passed through the left ventricle. Also present are typical findings of pulmonic valvular stenosis clearly visualizing the thickened stenotic valve and the poststenotic dilatation of the pulmonary artery. Selective angiocardiography with injection into the right ventricular outflow tract (Fig. 5) shows early opacification of the aorta. It is well known that when the pressure in the right ventricle is high, injection into the right ventricle can raise the pressure sufficiently to cause a right to left shunt through a ventricular septal defect; whereas if normal or moderately elevated right ventricular pressures are present, right ventricular outflow tract injection fails to produce a right to left shunt through that septal defect. There is no evidence of patent ductus arteriosus on the angiocardiograms.

Dr. Gasul: This has been a most interesting and instructive case study. It is interesting that clinical findings alone led us so close to an

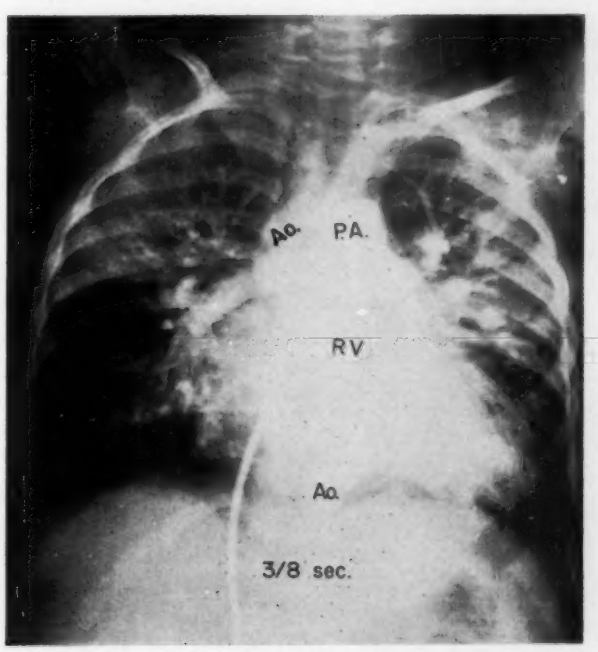


FIG. 5. *Selective angiocardiogram* with injection of the contrast substance into the right ventricle (RV). Note immediate opacification of the aorta (Ao.) simultaneously with the pulmonary arteries (PA).

accurate diagnosis. The phonocardiogram in this case was of great value. It demonstrated that what appeared to us on auscultation to be a loud second sound in the pulmonary area representing the aortic closure was in actuality a loud pulmonic closure, and that the aortic closure was buried in the loud murmur. Thus, the conventional readily available methods which require no hospitalization and no technically difficult procedures did establish the diagnosis. The findings on physical examination lead to the diagnosis of pulmonary valvular stenosis, but the x-ray films, demonstrating increased pulmonary blood flow, and the electrocardiogram suggesting right and left ventricular hypertrophy, pointed to a diagnosis of ventricular septal defect and pulmonary stenosis, e.g., acyanotic tetralogy of Fallot. Cardiac catheterization revealed the presence of pulmonary stenosis and a left to right shunt either at the ventricular or pulmonary level but the selective angiocardiogram into the right ventricular outflow tract established the presence of a ventricular septal defect. Although the diagnosis was established on clinical grounds alone, the presence of mild pulmonary arterial hypertension, causing the comparatively loud, and therefore, unusual closure of the pulmonic valve over the second left interspace, puzzled us greatly.

Operative Findings

Fifteen days after the conference the child was placed on a pump oxygenator and at cardiotomy a ventricular septal defect, 25 mm. in diameter, was found and repaired by Dr. Milton Weinberg, Jr. The defect was in an unusual location in the anterior superior portion of the ventricular septum where the crista supraventricularis is usually found. The pulmonary valves were greatly thickened, with some fusion of adjacent cusps, although the orifice permitted the passage of a finger with ease. The pulmonic valve ring appeared distinctly narrower than the adjacent pulmonary artery so that the presence of a large ventricular septal defect and a pulmonic valvular stenosis was established at surgery. The establishment of an accurate diagnosis was extremely important to this patient since surgery for pulmonic stenosis is frequently performed under hypothermia without the use of extracorporeal circulation. In this case the ventricular septal defect could not have been closed without the use of an extracorporeal circulation.

Historical Milestones

William Halsted on Refusion of Blood in Carbon Monoxide Poisoning (1883)

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IN ANALYZING the career of any great man it is usually instructive to examine the way in which he began his work. This principle can be applied with profit to the early researches of William S. Halsted, America's foremost investigator and teacher of surgery. The text which is reprinted herewith is Halsted's first published paper and describes the refusion (reinfusion) of blood as a treatment for carbon monoxide poisoning.

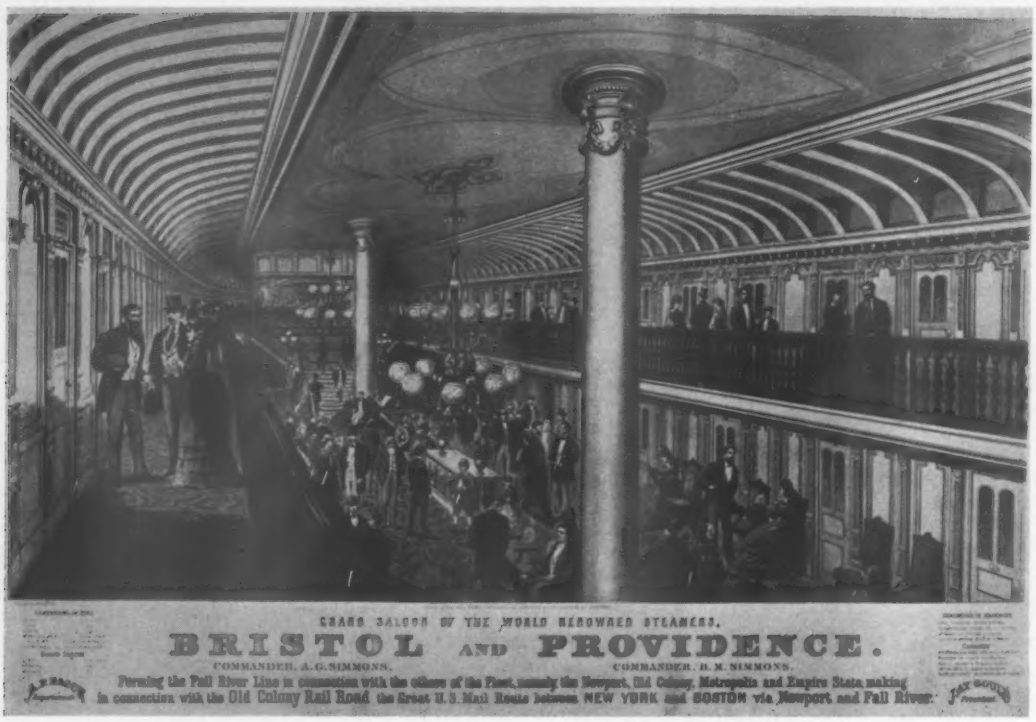
A few biographic facts will clarify the events which preceded the writing of the paper. For this purpose it is convenient to draw on the study which was written by Dr. W. G. MacCallum. William S. Halsted (1852–1922) was graduated from Yale College in 1874. He then entered the College of Physicians and Surgeons in New York, taking the doctoral degree three years later. While a medical student he acted as assistant to John C. Dalton, the physiologist. During his last student year he was surgical intern at Bellevue; after this he served for one year as house physician at New York Hospital. During 1878 to 1880 he visited Europe, where he studied with such famous men as Billroth, Mikulicz, Chiari and Kaposi. On returning to the United States he immediately undertook a large number of responsibilities, at the College of Physicians and Surgeons, the Charity Hospital at Blackwell's Island, The Emigrant Hospital at Ward's Island, Roosevelt Hospital, Bellevue Hospital, Presbyterian Hospital and the Chambers Street Hospital. He rapidly gained an impressive reputation as a teacher and operator. It was at Chambers Street Hospital, which had many cases of accidental and traumatic disease, that he made his experiments with refusion of blood.

The reader who is attentive to the special problems of hemodynamics will be interested in Halsted's views of the various types of centrifugal and centripetal infusion, just as the historian may wish to use the work as an indicator of the state of knowledge in 1883. However, the text of Halsted's paper offers more fundamental values than these.

The article shows several noteworthy traits. First, and most important, it evidences an inquiring mind, capable of discovering problems in the daily routine of clinical practice. Second, it shows a willingness to plan and execute a rational attack on such problems. Third, it shows at least a modest degree of originality. Fourth, it shows an adequate grasp of contemporary physiologic knowledge. Fifth, it clearly evinces a willingness to dig in the world's literature. Halsted stated elsewhere that "the idea of purifying and refunding the poisoned blood occurred to me on reading Hermann's Physiology."* How many young American surgeons today read German treatises on physiology or any other subject? Sixth, Halsted's paper shows a sufficient command of foreign languages and an adequate command of English. Seventh, it demonstrates detailed observation and recording, combined with the candor which reports failures as well as successes. Let today's aspiring clinician test himself against this checklist of traits and profit as well as he can.

The article which is reprinted herein was

* HALSTED, W. S. Discussion of paper by Edward J. Klopp, "Refusion of Blood in Haemorrhage." *Tr. Am. Surg. Assoc.*, 40: 218, 1922. Reprinted in Surgical Papers by William Stewart Halsted, edited by Walter C. Burket, vol. 1, p. 14, Baltimore, 1924. Johns Hopkins Press. See also: HERMANN, L. Grundriss der Physiologie des Menschen, 4th ed., Berlin, 1872. Hirschwald.


GRAND SALOON OF THE WORLD RENOWNED STEAMERS.
BRISTOL AND PROVIDENCE.
COMMANDER, A. G. SIMMONS.
COMMANDER, R. M. SIMMONS.
Forming the Fall River Line in connection with the others of the Fleet, namely the Newport, Old Colony, Metropolis and Empire State making
in connection with the Old Colony Rail Road the Great U. S. Mail Route between NEW YORK and BOSTON via Newport and Fall River.

This illustration shows the elaborate decoration characteristic of the Age of Elegance. *Note the gaslights.* Courtesy of The Mariners Museum, Newport News, Virginia.

first published, under the title, "Refusion in Carbonic-Oxide Poisoning," in the *New York Medical Journal*, volume 38, pages 625 to 629, 1883. It also appeared in *Medical News*, volume 43, pages 622 to 626, 1883, in the *Annals of Anatomy and Surgery*, volume 9, pages 7 to 21, 1884, and in Halsted's Collected Surgical Papers, which was edited by Walter C. Burket and published in two volumes by the Johns Hopkins Press in 1924. Slight differences are detectable in the various versions. The text used in the present reprint is that of the *New York Medical Journal*.

* * *

Halsted on Refusion of Blood

Contributions to the treatment of patients poisoned by carbonic oxide, the most noxious constituent of coal and illuminating gases, are especially worthy of consideration because of the great frequency of and mortality from this form of poisoning. In Adolph Lesser's[1] tables carbonic oxide figures as the most common poison, and the one which yields the highest percentage of fatal cases.

Refusion of blood is literally a depletory transfusion, in which the blood withdrawn is returned to the circulation of the loser. Volkmann,[2] in discussing exarticulation at the hip joint, suggests the feasibility of catching the blood lost, peradventure, in this operation, and returning it to the loser through the divided femoral vein. And Esmarch[3] has, in one instance, endeavored to act in accordance with Volkmann's suggestion, but his patient died while preparations were being made for transfusion. Hueter,[4] in frost-gangrene of both feet, transfused centrifugally 350 cc. of the patient's own blood, defibrinated, into the left posterior tibial artery, and believed that he thereby preserved a portion of the frozen part. The right foot, untransfused, underwent an extensive forfeiture.

Highmore,[5] evidently not aware that it had already occurred to others to refund blood, offers "remarks on an overlooked source of blood supply for transfusion in postpartum haemorrhage," and recommends utilizing the

[1] Virchow's "Archiv," lxxxiii, 2, 1881, p. 193.

[2] R. Volkmann. Drei Fälle von Exarticulation des Oberschenkels im Hüftgelenk." "Deutsche Klinik," 1868, p. 382.

[3] H. Leisrink. "Ueber die Transfusion des Blutes." Volkmann's "Sammlung klinischer Vorträge," No. 41. Landois, "Die Transfusion des Blutes," p. 327.

[4] E. Peters. "Die arterielle Transfusion und ihre Anwendung bei Erfrierung," Greifswald, 1874.

[5] "Lancet," London, 1874, i, p. 89.

blood lost by the mother. Other than these I know of no hints or attempts at refusion.

In carbonic-oxide poisoning, refusion involves an additional factor, viz.: the oxygenation of the poisoned blood employed; and is, therefore, an infusion of the purified, defibrinated for the poisoned, entire blood of the individual.

A most radical case of refusion is the following:

On the 5th of last May, Mr. A. S. G., aged fifty-seven, a man of medium size and good physique, was found unconscious in a state-room of the steamer Bristol by the ticket-taker, who observed a strong smell of gas in the room. He was taken in an ambulance to the Chambers Street Hospital, where he arrived at 9.05 A.M. The house-surgeon states that, on admission, the patient could not be aroused. Respirations superficial; pulse fairly strong, and 85 beats a minute; temperature not taken. Skin pale and cold; lips slate-colored; pupils somewhat dilated. Was put in a hot-air bath and given whisky hypodermically. At 10.30 A.M., when I first saw the patient, he was still comatose. His eyes were partly open, and his pupils equal, slightly contracted, and irresponsive to light; face ashy pale, and surface of body cold. The respirations, 28 a minute, were abdominal and so superficial that it was almost impossible to count them; pulse 96, small and easily compressible. Feeble conjunctival and plantar reflexes; other superficial reflexes absent, except cremasteric on left side. Deep reflexes could not be tested because of the rigidity which existed. Both arms were flexed; the right more strongly than the left. 10.50 A.M.: right radial artery exposed above wrist for about one inch, and two ligatures passed under it.

A cannula, introduced centripetally into the artery, was held in place by one ligature; the other was used to occlude the vessel peripherally. Through the cannula 512 c.c. of blood were withdrawn, defibrinated, strained and kept at a temperature of about 37.5° C. in a transfusion apparatus similar to that which is before you. 11.20 A.M.: temperature 35.4° C. (95.8° F.), pulse 92, respiration 22, full and dyspnoeic. Superficial reflexes well pronounced. Eyes closed, but patient can be made to open them. Rigidity of limbs has, in great measure, disappeared. 11.32 A.M., 288 c.c. of defibrinated blood, all that could be obtained from the 512 c.cm., were refunded through the cannula in the artery toward the heart—centripetal arterial infusion. At 11.45 the injection was completed. Temperature 36.6° C. (98° F.), pulse 104, respirations 28, deep and labored. Superficial reflexes possibly exaggerated. The usual post-transfusion rigors lasted for half an hour. 12.35 P.M.: 300 c.c. withdrawn, as before, through the cannula, defibrinated and mixed with 128 c.c. of defibrinated blood taken from another patient. 1 P.M.: temperature 38.2° C. (100.8° F.), pulse 128, respiration 28. 1.05 P.M.: patient's pallor most striking; 192 c.c. of the mixed blood infused. The color returned rapidly to his face when from 80 to 100 c.c. had been injected, the change from a deathly white to a healthy red taking place in a few seconds. 1.13: temperature 39.1°, pulse 120, respiration 40. 2.30: temperature 39.4°, pulse 140, respiration 40. 5.20: temperature 37.8°, pulse 116, respiration 20.

Patient has been gradually returning to consciousness since the first venesection, and now attempts to get out of bed.

May 6th.—12.15 P.M.: urine voided voluntarily for the first time since admission, it having previously been drawn with a catheter.

8.20 A.M.: temperature 37° (normal), pulse 98, respirations 20. Patient in good condition, but mentally still a little dull. 4.30 P.M.: patient eats well, and desires to go home.

May 7th.—Intellect perfectly clear; remembers that the steward lighted the gas in his state-room about 9.30 P.M., the night previous to his poisoning, but that it went out as the door was closed. Undressed himself in the dark, went to bed, and can recall nothing of the night. Has experienced none of the unpleasant after-effects of the poisoning.

Allowed to go home to Wareham, Mass., about 50 hours after admission. . . . October 24th, have today, $5^1/_2$ months after the poisoning, interviewed Mr. A. S. G., and ascertained that he has not had a single unpleasant symptom referable to the effect of the gas.

That this patient would have recovered without such active treatment is not improbable. It is, nevertheless, certain that the blood-letting exerted a most favorable influence, changing almost instantly the entire aspect of the case. The scarcely perceptible respirations became at once conspicuously full; in a few moments the absent superficial reflexes had returned and the rigid arms relaxed. The body-surface grew gradually warmer, and,

after the first infusion, the temperature had risen from 35.4° to 36.6° C. The pulse and respirations kept pace with the temperature. The first infusion prepared the subject for a second depletion, and contributed to the rise in temperature, and, probably, to the improved circulation. The second infusion was decidedly indicated, as evidenced by the impression it produced in the patient's color.

In the light of Kühne's[6] experiments on animals, it is a question whether the bloodletting alone would not have rescued all the cases of carbonic-oxide poisoning in the human subject in which a depletory transfusion has been successful. Kühne (*loc. cit.*) has found that venesection of itself could save life if the respirations were as much as two in a minute. From twenty-three cases of transfusion for carbonic-oxide poisoning, of which I have notes, twelve terminated favorably. In two (Casse,[7] one; Lühe,[8] one) of the twelve successful cases very small quantities of blood were transfused, and without any immediate good effects. In one (Hüter[9]) of the remaining cases attempts at depletion were unsuccessful, only a few drops of blood having been withdrawn. In three cases (Garrigues,[10] one; Halsted, two) the venesection exerted a decidedly favorable influence. Three cases (Badt,[11] one; Martin,[12] one; Lehmann,[13] one) are narrated in articles to which I have not access, and so can not arrive at any positive conclusions as to which was the more efficatious agent, the venesection or the transfusion. In one case (König[14]) the venesection (the amount of blood withdrawn is not stated) was attended with slight, and the transfusion with no success. The two remaining cases (Jürgensen,[15] one; Saltzmann,[16] one) were apparently benefited by the transfusion, and yet in neither is any reference made to the influence of the depletion, although from one (Jürgensen) 400 c.c., and from the other (Saltzmann) 180 c.cm., of blood were abstracted.

Some, then, of the cases claimed for transfusion seem attributable to the venesection which preceded it; and in no instance has it seemed to me clearly demonstrable that transfusion has saved life where venesection had failed.

A few cases are reported by O. Kahler,[17] Marten,[18] and others,[19] of venesection in carboxysmus with good results. And, of the several cases which have come under my care, I will cite briefly, in proof of the efficacy of venesection, the most serious (one in which depletory transfusion was resorted to):

On May 5, 1882, at 10.10 A.M., Lillie Bent, a robust girl of seventeen, was admitted to Chambers Street Hospital, suffering from illuminating-gas poisoning. The night before, on retiring, she is supposed to have blown out the gas in her state-room on the steamer Providence.

On admission, she is said to have been unconscious, moaning, and much cyanosed. Her respirations were shallow, and her pulse rapid and feeble. Temperature not taken.

Whisky and digitalis were given hypodermically. She was put in a hot-air bath and hot cloths were applied to the praecordia. Flagellation and the inhalation of ammonia would partially arouse her. Artificial respiration was tried, but with what effect is not stated. She would improve temporarily under the treatment, but when left alone returned to her previous condition.

I saw her about 5 P.M. Her temperature was 39.1° C., respiration 40, and pulse 120. Advised washing the stomach and large intestine with hot water for the purpose of further stimulation.

9 P.M.: Patient much worse. Pulse feeble, more rapid and intermittent; respirations very superficial; conjunctivae insensitive and all reflexes absent; mouth frothy; occasional facial twitchings and grinding of the teeth;

[6] "Centralblatt f. Chir.," 1864, No. 9.

[7] "Presse méd.," xxviii, 8, 1876.

[8] Transfusion bei Kohlenoxyd Vergiftung mit günstigem Ausgang. "Deutsche mil. aertzl. Ztschr.," Berlin, 1878, vii, 263–267.

[9] "Berl. klin. Wochenschr.," 1870, No. 28.

[10] "New York Med. Journal," March 3, 1883.

[11] Badt, "Verhandlungen der Berl. med. Gesellschaft," i, 1866.

[12] Massmann (B.W.), "Beiträge zur Casuistik der Transfusion des Blutes," Berlin, 1870.

[13] Massmann (*loc. cit.*).

[14] Evers, "Deutsche Klinik," 8, 9, and 10, 1870.

[15] "Berl. klin. Wochenschr.," 1870.

[16] Fall of höggradig Kolosforgiftning, behandladt med. Transfusion. "Finska Läkaresällskapets Handl.," Bd. 19, p. 266.

[17] O. Kahler, Virchow's "Jahresb.," 1881, 1, p. 420.

[18] Marten, "Vjhrschr. f.g. Med.," xxv, 1864, pp. 197–224.

[19] Henrick Jensen, in Helsingör, "Hospitals-Tidende," 2, R. 1, 25, 26, 1874, reports a case of carbonic-oxide poisoning which is interesting from the fact that decided reaction was observed during a brief menstruation. (Strange that venesection was not suggested to him by this occurrence.) Lauz in Biel, "Schweiz. Corr. Bl." i, 12, p. 324, 1871.

arms and legs rigid—the flexor muscles overpowering the extensors.

9.05 P.M.: 204 c.c. of blood withdrawn from left basilic vein; upon this the condition of the patient improved marvelously; almost instantly her respirations became full and her pulse strong and less rapid. The rigidity of her limbs disappeared, her reflexes returned, and she could be aroused by shaking or speaking loudly to her.

11 P.M.: Attempted to transfuse entire blood from a Behier's apparatus into patient's right cephalic vein, but failed to introduce more than 30 c.c.

May 6th.—During the night nourishment was administered per rectum. At 6 A.M. patient answers questions somewhat intelligently, and at 9 A.M. takes nourishment by the mouth.

It is difficult in any case to know precisely how much of the cure should be attributed to the treatment. When, however, a case like the one just narrated, observed sufficiently long to exclude fluctuation, assumes a decidedly more serious aspect, and then is, almost instantly, on treatment, transformed into rapid convalescence, one feels justified in assigning a cause to the effect.

Many apparently severe cases of carbonic-oxide poisoning are recorded, which have recovered more or less promptly when exposed to fresh air and stimulation. Some, too, where oxygen[20] is believed to have hastened the convalescence. But if, despite these measures, the patient's condition grows constantly worse, death is virtually certain, unless venesection be resorted to.

From the hour of her admission until she was bled—eleven hours—Lillie Bent's condition was growing gradually worse, and ultimately became so bad that her case seemed hopeless; this, in a moment, upon venesection, was transformed into one of apparently certain recovery.

The transfusion produced no appreciable effect, as might have been expected from the small amount of blood injected.

As additional proof of the value of bleeding in carbonic-oxide poisoning I might allude to the case of her illicit companion, who, occupying the state-room with her, was likewise poisoned. Less seriously affected by the gas, he was venesected while convalescing. Maniacal and confined in a strait-jacket, he was bled about 512 c.c., and thereupon became so rational and docile that it was no longer necessary to restrain him.

To cite, as I might, other less serious cases in which the beneficial effect of blood-letting was less strikingly apparent would be superfluous.

Why, then, transfuse if venesection accomplishes so much? If for no other reason, to allow of repeated venesection. The poisoned individual should be bled freely, unless there be decided contraindications, even after, to all appearances, out of danger, in the hope of diminishing the risk of pernicious after-effects.

Although bleeding of itself will probably suffice to save life in almost all cases which occur in practice, it has been demonstrated by Kühne (*l.c.*) that animals, poisoned beyond hope of rescue by venesection, can be saved by transfusion. In one of his experiments, where respiration had been suspended seven minutes, he was still able to restore life to the animal by the infusion of defibrinated blood.

Aside from experimental demonstrations of the value of transfusion in cases beyond recall by means of bleeding, nothing could be theoretically much more enticing than the plausibility of *substituting* blood corpuscles capable of taking up oxygen for such as are incapacitated from so doing by reason of the somewhat stable compound which carbonic oxide forms with their haemoglobin. Thus the much quoted and meritorious experiments of Panum[21] have led his partisans to believe in the possibility of blood *substitution* and to regard the blood corpuscles as something which can be taken from one individual and *transplanted* in another.

But von Ott[22] has shown the falsity of Panum's deductions, inasmuch as he could obtain like results, although making use of a fluid which contained no morphological elements.

Von Ott (*l.c.*) has demonstrated, furthermore, that blood corpuscles infused into the circulation are short lived, and that blood, whether entire or defibrinated, for other reasons, is not only no better than but not as good as a 0.06-per cent saline solution for

[20] Virchow's "Jahresb.," 1869, i. p. 320. Alonzo Clark, "Two Cases of Poisoning with Illuminating Gas successfully treated by the Inhalation of Oxygen." "New York Med. Jour.," August 11, 1883. Lockey Stewart, "Brit. Med. Jour." September 25, 1875, p. 392. Case of carbonic-oxide poisoning in which the inhalation of oxygen exerted no influence upon the patient's condition.

[21] "Archiv. f. path. Anat. u. Phys. u. f. klin. Med.," 1863.

[22] *Ibid.*, 1883, p. 114.

transfusion in acute anaemia. One can not, therefore, properly speak of a substitution as transplantation of blood corpuscles by infusion of them into an impoverished circulation.

Fortunately, however, in carbonic-oxide poisoning it is merely necessary to sustain the patient artificially for a brief period, and for this, undoubtedly, the infused corpuscles can serve as oxygen carriers for a sufficiently long time. For the circumstance, as von Ott's (*l.c.*) experiments teach us, that the infused corpuscles do not become integral constituents of the new organism, but rather are destined to a more or less rapid disintegration and elimination, does not prevent them from circulating and temporarily taking part in the interchange of gases. Clear, then, as are the indications for transfusion auxiliary to venesection in the treatment of the cases under consideration, the extreme difficulty of obtaining blood at all, to say nothing of sufficient quantity, has, up to the present time, classified the operation with the rarer therapeutic procedures. And we might, indeed, in the treatment of these cases, content ourselves with blood-letting were it not that the practicability of *refusion* removes what has been, perhaps, the greatest obstacle to the performance of transfusion.

To the investigations of Hermann, Donders,[23] and Podolinski[24] I owe the conception of refunding the purified for the poisoned blood of the victim to carbonic-oxide poisoning. Hermann[25] calls attention to the fact that nitrogen monoxide can liberate the carbonic oxide of the carbonoxy-haemoglobin, and forms a stronger combination with haemoglobin than carbonic oxide does; and, subsequently, Donders (*l.c.*), Hermann, and Podolinski (*l.c.*) find that oxygen or air can, in a few minutes, free haemoglobin from carbonic oxide if passed forcibly and in large quantities through the poisoned blood.

As to the best method of infusing fluids into the circulation, good authorities disagree. Of the four possible methods, centrifugally or centripetally into an artery or vein, the question of centrifugal venous infusion is entertained only to be discarded. Hueter, who gives to von Graefe the honor of being the first to draw attention to centrifugal arterial transfusion, deserves the credit of having introduced it to the profession, and strongly advocated the method.

[23] "Archiv. f. Phys." v, p. 24.
[24] *Ibid.*, vi, p. 553.
[25] "Arch für Anat. und Phys.," 1869.

Landois,[26] too, while contrasting, in general, arterial with venous transfusion, prefers, from a physiological standpoint, the arterial, be it centripetal or centrifugal.

Cohnheim,[27] on the other hand, expresses himself decidedly against centrifugal arterial transfusion essentially as follows: One should surely under no circumstances inject peripherally into an artery; for the peripheral arterial branches contract with such energy against the foreign blood which is entering them that it is often necessary, in order to overcome the resistance, to exercise pressure sufficiently forcible to rupture the blood-vessels. The case is very different when one injects centripetally into an artery and employs no more pressure than is required to overcome the existing arterial tension. The blood infused mingles at once with that which is already present in the artery and flows, without resistance, into the first branch above, thence into its arterial and capillary ramifications, and from here on, under normal venous pressure, to the heart.

Kümmel,[28] Schede's assistant, produced gangrene of the hand by the centrifugal infusion of a saline solution into the radial artery, thus giving us a demonstration of a disaster which may attend this method, and which he might have foreseen.

We are, then, restricted to the choice between centripetal arterial and centripetal venous infusion.

Hüter's[29] arguments for peripheral or centrifugal arterial transfusion hold good for centripetal arterial infusion. He prefers the arterial to the venous transfusion, because the blood by the former method courses slower and more uniformly to the heart; because the minutest air-vesicle is retained in the capillaries; and because the danger of phlebitis is avoided.

Landois (*l.c.*) adds to these advantages another, viz.: that the capillary system, like a supplementary filter, catches all foreign particles which may be present.

The essential advantages of centripetal arterial transfusion in profound asphyxia, says Landois (*l.c.*), can be summed up as follows: 1. Arterial blood is thus most directly dispatched to the nerve-centers, in consequence of which the

[26] "Die Transfusion des Blutes," Leipzig, 1875.
[27] "Vorlesungen über allegemeine Pathologie," Bd. i, p. 424.
[28] "Centralblatt f. Chir.," 1882, No. 19.
[29] Langenbeck's "Archiv," Bd. xii.

venous blood there contained is propelled onward into the veins; and 2. The filling of the arterial system rejuvenates the feeble circulation by creating a considerable difference in pressure between the arterial and venous systems.

Cohnheim (*l.c.*), too, from his experiments on animals, declares the central or centripetal arterial transfusion to be the least dangerous, and at the same time most completely effectual procedure.

From a practical standpoint, I am also impelled to advocate centripetal arterial infusion.

Besides the case already narrated, it has been my good fortune to transfuse by this method with most brilliant and unexpected success in two cases—one of acute anaemia and one of septicaemia.

Joseph Hart, aged eleven years, was admitted to Roosevelt Hospital, September 15, 1882, for a compound comminuted fracture of the tibia and some of the tarsal bones. The ankle joint was involved in the injury, and the soft parts were badly mangled. The wheel of a street-car had passed over his leg the night before. Patient is said to have lost much blood, and the cloths in which his leg was wrapped furnished evidence to that effect. The parents would not consent to an amputation, and the boy, although perfectly conscious and able to give an account of himself, was not in condition for it.

At 8.30 P.M.—eleven or twelve hours after admission—the patient was cold and unconscious, and his pulse was so rapid and feeble that it could not be counted satisfactorily. It was estimated to be 180 per minute. I injected 192 c.c. of a salt solution (chloride of sodium ʒj; water, o.j) centripetally into the left radial artery, whereupon the pulse became quite full, and 135 a minute. The boy regained consciousness immediately, and his condition seemed to warrant an attempt at amputation—permission to do so having, meanwhile, been obtained. The administration of ether had such a bad effect on the pulse that the operation was deferred, and the leg placed in a hot-water bath. The patient continued to improve, and survived an amputation of the leg, performed by Dr. Sands, twenty-five days after admission.

On the 18th of March, 1883, at Ward's Island, I infused defibrinated blood centripetally into the radial artery, in a case of septicaemia.

The patient, an Italian, about forty years of age, had suffered for several months from a suppurative disease of the ankle and some of the tarsal joints. For about one week prior to the operation he had, almost daily, well-pronounced rigors and a temperature ranging from about 36.1° C. (97° F.) to 40.6° C. (105° F.). He was so feeble that to amputate was deemed inadvisable even as a last resort. A depletory transfusion was accordingly undertaken. A stout philanthropic German offered to furnish the blood. So plentiful was his subcutaneous fat that not a vein could be seen, although his arm had been carefully constricted below the point at which the basilic vein usually perforates the deep fascia. Dissection for a vein, prolonged until even the would-be donor appeared willing to have the search discontinued, failed to discover one. Thereupon the radial artery was exposed without difficulty, although our subject fainted as the incision was being made through the integument, and so necessitated the completion of the operation upon the floor. The Italian was next depleted through his right radial artery until the arterial tension was barely sufficient to throw a jet across the graduated jar, into which 178 c.c. had been allowed to flow.

Immediately thereupon 186 c.c. of defibrinated blood was infused centripetally into the artery. In a few moments the patient's pulse had fallen to 120, which was eight beats better to the minute than before the administration of ether. The leg was then amputated just below its middle. Patient's pulse 112–114, weak, but regular, and better than before the amputation.

Cardiac stimulants were, of course, freely administered. Slight post-transfusion rigor and a temperature of 38.8° C. On the following morning, March 19th, patient's pulse was 110, and temperature normal. Since then uninterrupted convalescence.

It is only just to add that I have once done centripetal arterial infusion, in a desperate case of pyaemia, where the fatal termination was probably precipitated by the operation.

If the infusion of defibrinated blood influenced the action of the heart unfavorably, it certainly was, in part, to be explained by the too heroic depletion which preceded it.

This unsuccessful attempt should not militate against the method of injecting the blood, but rather against the indication for so doing, or against the manner or extent of depletion.

The main argument of those who prefer centripetal venous to centripetal arterial infusion is that the former is the simpler. If it be true that the latter is, in any degree, the safer method, the simplicity of the former does not deserve to be considered. Furthermore, instead of being easier, I am sure that it is often more difficult to discover a vein than to expose the radial artery. It was, for instance, impossible to discover a vein in the stout German referred to in this paper. Jennings,[30] too, one of the more recent advocates of the intravenous method, without having practiced the arterial, had considerable difficulty in finding a vein in one instance, and others testify to the same experience. The dangers of intravenous infusion, such as the introduction of air and small clots, and the overpowering of the heart by a too rapid injection, may be, theoretically, easy to avoid, but, practically, death has frequently been brought about by one or more of these causes.

To the centripetal arterial infusion pertain, theoretically, none of the dangers which, practically, in the intravenous method, are far from always to be avoided. And, from a practical stand-point, my cases, which, I believe, are the first recorded, induce me to advocate the centripetal arterial method.

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Author's Comments

The first trait which impresses the reader of Halsted's article is the economy of the presentation. The case histories are limited to the relevant details. Reports of physical examination dwell largely on the general appearance of the patients and on the condition of the neuromuscular system. There is a total absence of laboratory data: there are no blood tests and, of course, no readings of blood pressure and no cardiograms.

The therapeutic measures were likewise extremely simple. Aside from refusion and one infusion of saline solution, the treatments consisted of whisky (injected hypodermically!), catheterization, injections of digitalis, nutrient enemata and inhalations of ammonia. Transfusion was of course given without blood-typing. There is mention of the "usual post-transfusion rigors."

Halsted is honest enough to point out that venesection alone would probably save most persons poisoned by carbon monoxide. He believed that venesection followed by refusion permitted the removal of greater quantities of poisoned blood than was possible with venesection alone. He gives an interesting summary of the administration of blood into veins and arteries, centripetally and centrifugally. This part of his work has increased in practical value as a result of recent advances in medical and surgical treatment of cardiovascular disease. He believed that if blood injected into an artery is directed centripetally, i.e. against the current, it is less likely to cause vascular spasm and gangrene than if injected centrifugally.

In addition to its technical aspects this paper is open to a number of sociologic inferences. In studying the work of any physician it is important to consider who his patients were and how they entered the orbit of medical attention. The resolution of this problem in the present instance may prove interesting to our readers. Fortunately Halsted's text provides a few clues.

His second patient is said to have been a robust seventeen year old girl named Lillie Bent, who was overcome by gas on the steamer Providence on May 4, 1882, and was admitted to the Chambers Street Hospital on the following morning. The Chambers Street Hospital was torn down in 1894; to the present time I have been unable to find its records. After describing Miss Bent's case Halsted goes on to tell of "her illicit companion, who, occupying the stateroom with her, was likewise poisoned." The word "illicit" was deleted when the article was republished in the *Annals of Anatomy and Surgery* in 1884. Thus we have the case of a man who illicitly occupied a stateroom with a robust seventeen year old girl. This does not give the impression of a voyage on a luxurious transatlantic liner. Instead it conforms with the pattern of overnight liaison on an excursion boat. The name "Providence" suggested the famous Fall River Line. A study of "The Old Fall River Line" by Mc Adam immediately confirmed this hypothesis.*

According to Mr. Mc Adam, the Providence and the Bristol, luxury ships owned by the expansive Jim Fisk were launched at New York in 1866 and commissioned in 1867. Each had an over-all length of 373 feet and gross tonnage of nearly 3,000. They were equipped with such extravagant appurtenances as brass bands,

[30] "Transfusion," p. 26. Baillière, Tindall & Cox, London, 1883.

* Mc Adam, R. W. The Old Fall River Line. Revised edition. New York, 1955, Stephen Daye Press, 288 pp. See also: Jensen, O. The Old Fall River Line, American Heritage, 6 (1): 6, 1954.

fancy carpeting and caged canaries. More relevantly, they were illuminated by gas. The entire mise-en-scene was part of the American Age of Elegance.

The accidents which provided Halsted with his cases were reported in the newspapers. Thus the *New York Times* of May 6, 1882, carried the following article:

SUFFOCATED BY GAS

A man and a woman who appeared to be man and wife took passage on the Sound steamer Providence, of the Fall River Line, at Fall River, Mass., Thursday evening (May 4). They were assigned to outer stateroom No. 147, on the starboard side aft. Twice before the arrival of the boat at its pier, No. 28, North River, yesterday morning, the purser rapped at their door to obtain their tickets, but received no response. At 9 o'clock a third effort was made to arouse the occupants of the stateroom, but without success. Knowing that something was wrong, the boat's carpenter was summoned by Capt. Simmons to effect an entrance. The blind was removed, and the carpenter, crawling through the window, opened the door. The man and the woman were found lying in the lower berth, both ashy pale and insensible, and it was at first thought dead. A light breathing was however discerned and the cause of their condition was looked for. The smell of gas was perceptible, and an examination showed that the jet in the stateroom was turned on full head. The man and the woman were removed to the Chambers Street Hospital, and it was regarded as a question of life and death with them for a long time. The man regained consciousness at 5 o'clock in the afternoon but at a late hour last night his mind was still wandering and he talked incoherently. The woman at midnight was still insensible, and will probably die. Papers found in the pocketbook of the man prove him to be Emilio Corsi, of the firm of Corsi and Rebholtz, fresco and decorative painters, No. 5 Fenner Street, Providence, R. I. A letter written to Corsi by the woman discloses her identity. Her name is Lillie Bent, and her home is in West Falmouth, Mass. The letter is dated West Falmouth, May 3, and was sent to Wood's Hole, Mass., where Corsi must have been stopping. It made an appointment to meet Corsi at a railroad station Thursday, presumably to make the trip to New-York.

Mr. C. A. Collins, III, of the Rhode Island Historical Society has kindly informed me that the firm of Corsi and Rebholtz, painters, is recorded in the Providence Directory for the years 1882 and 1883 but not subsequently.

Halsted's first patient, Mr. A. S. G., was also traced by means of the newspapers, although there are minor discrepancies in the reports. He proved to be Mr. Ansel S. Gurney, a grain merchant of Wareham, Massachusetts. A certain flippancy is evident in the newspaper accounts since the *New York Tribune* titled its article "A Massachusetts Man Blows Out the Gas," while the *New York Herald* used the caption "Does Not Read the Papers." These articles appeared on May 16, 1883, and state the accident to have occurred on May 15. Thus some of the dates given by Halsted in his case notes are in error. There are, likewise, a few errors in the newpaper notices, chiefly as regards the spelling of names.

Through the courtesy of Mr. Burton M. Tripp, Chief of Police, Marion, Massachusetts, it was learned that Mr. Gurney died on May 28, 1904, at the age of eight-one years and five months. Thus he survived the poisoning by twenty-one years. Mr. Tripp placed me in communication with Miss Lovicy M. Delano of Marion, Massachusetts, who kindly supplied confirmatory information. Miss Delano is Mr. Gurney's granddaughter; she states that Mr. Gurney was a grain merchant and usually captained his own ship to obtain grain in New York. It is her opinion that the accident was caused by the wind blowing out the gaslight in Mr. Gurney's stateroom.

ACKNOWLEDGMENT

The author wishes to express appreciation to the following persons and institutions for information and other assistance: Miss E. Marie Becker of the New York Historical Society; Dr. and Mrs. Henry S. Huber; The Mariners Museum, Newport News, Virginia; the *New York Times;* Mr. Burton M. Tripp, Chief of Police, Marion, Massachusetts; and Miss Lovicy M. Delano, Marion, Massachusetts.

Case Reports

Evolution of Ventricular Septal Defect and Pulmonary Stenosis with Left to Right Shunt into Classic Tetralogy of Fallot

A Case Report with Clinical, Angiocardiographic and Anatomic Correlations*

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THIS report is a comment on the clinical, angiocardiographic and pathologic features of a case of a patient with congenital heart disease. The clinical course of this patient illustrates the behavior in some cases of a particular type of ventricular septal defect and a distortion of the ostium infundibuli in which the picture of the tetralogy of Fallot previously absent develops after a period of time. The angiocardiographic and pathologic findings demonstrate the anatomic basis for such a changing clinical pattern related to the formation of subendocardial fibrosis on the displaced muscle bundles at the ostium infundibuli.

CASE REPORT

A. K., four month old girl, was first seen in the cardiac outpatient department of the Pediatric Clinic of the Karolinska sjukhuset in December 1958. She was referred to this department because of a murmur first discovered in the maternity hospital. Gestation was reported as having been normal and the labor uneventful. The child had a history of slight dyspnea and sweating usually after feedings.

Physical examination revealed a normally developed infant (body weight 6.03 kg.) without cyanosis. She had a respiratory rate of about 80 to 100 per minute. The liver was palpable 2 to 3 cm. below the right costal margin. The femoral pulses were palpable. A rough systolic murmur of grade 5 was heard over the whole precordium with the maximal intensity at the third and fourth left intercostal spaces. A systolic thrill was felt in the same area. The second sound over the second left intercostal space was diminished, suggesting pulmonary stenosis. An apical middiastolic murmur was also heard. The *electrocardiogram* (Fig. 1) showed an electrical axis of +75° to +80° and signs of right ventricular hypertrophy.

Roentgenologic examination of the chest (Fig. 2) showed the relative heart volume (absolute roentgenologic volume related to body surface area) to be 450 cc. The average normal relative heart size in this age is 220 cc. The heart revealed evidence of right ventricular enlargement as well as left atrial dilatation and left ventricular enlargement. The aortic arch was on the left side. The pulmonary artery was not well outlined but some dilatation was suggested because its hilar and peripheral branches were wide. The aorta was of normal size. These findings indicated the presence of a left to right shunt, presumably through a ventricular septal defect. Except for the engorgement of the pulmonary vessels there were no pathologic findings in the lungs.

Cardiac Catheterization: The clinical findings in combination with the roentgenographic picture raised the suspicion of a ventricular septal defect combined with pulmonary stenosis. With this tentative diagnosis, the child was admitted to the hospital on January 20, 1959 for further investigation and treatment. Heart catheterization was performed

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using general anesthesia with tribromoethanol. The results are presented in Table 1.

A systolic pressure gradient of 62 mm. Hg between the pulmonary artery and the right ventricle (20/7 and 82/8 mm. Hg, respectively) with a normal wedge pressure was noted. The systemic pressure by cuff was 70/50 mm. Hg. There were clear signs of a left to right shunt at the ventricular level with an oxygen difference of 1.7 vol. per cent between the superior vena cava and the pulmonary artery. There was a 91 per cent saturation of the femoral arterial blood when the child was breathing room air.

Angiocardiography: A selective angiocardiography was performed in connection with cardiac catheterization. The contrast medium was injected into the right ventricle. Rapid serial depiction took place in two planes simultaneously (Elema roll film changer, Gidlund system). The exposures were marked on a synchronously recording electrocardiogram. The right ventricle was slightly enlarged and showed increased trabeculation. The infundibulum and particularly the ostium infundibuli were moderately distorted by a displaced crista supraventricularis with anterior and upward shift of the parietal band and slight dislocation of the septal band (Figs. 3 and 4). This caused the ostium infundibuli to be moderately narrowed. The contrast medium spread rapidly into the left ventricle through a septal defect located below the crista. These structures were well outlined. The absence of septal tissue below the right aortic cusp suggested that the defect extended anterior to the papillary muscle of the conus. There was no obvious overriding of the aorta. The pulmonary artery was slightly wider than normal and its branches were insignificantly dilated. The pulmonary valves were not thickened. After having visualized the left

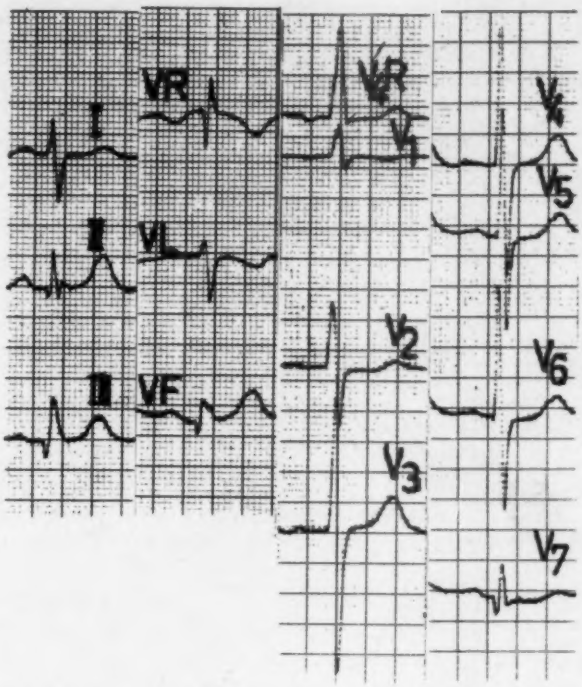

FIG. 1. Electrocardiogram during the first examination at the age of four months. Electrical axis +80° and signs of right ventricular hypertrophy.

atrium and the left ventricle which were both dilated, the medium reappeared in the right ventricle. This was due to a left to right shunt through the ventricular septal defect. The aorta was apparently of normal caliber.

Clinical Course: The patient was digitalized; her general condition improved and the enlargement of the liver disappeared. An operation with complete

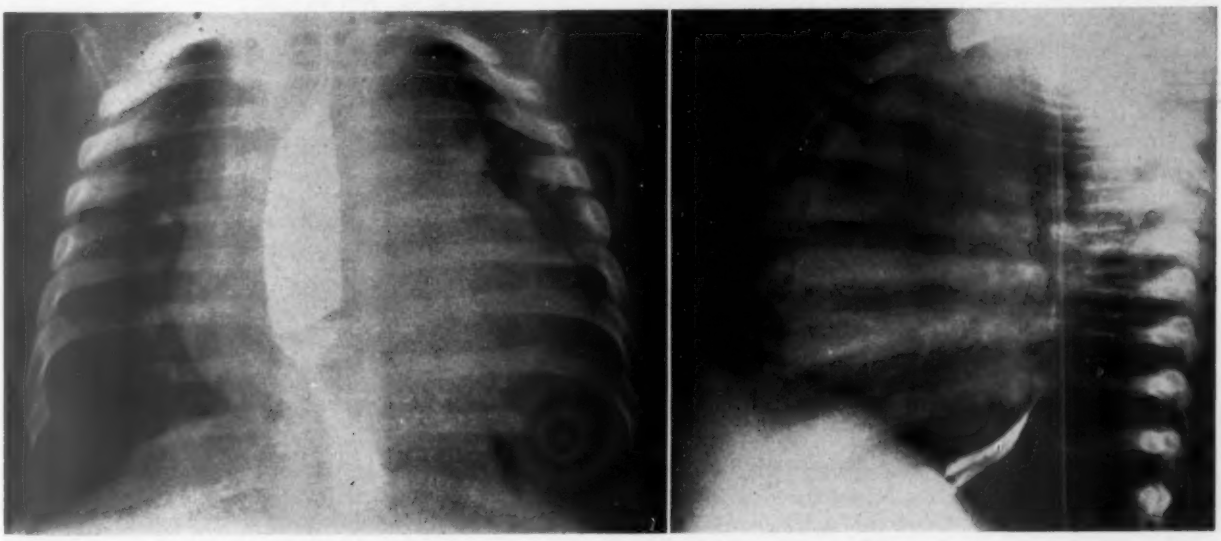

FIG. 2. Roentgenograms at age four months in P-A and lateral views. The heart is enlarged. Roentgenologic heart volume related to body surface area is 450 cc. Average normal value is 220 cc. There are signs of ventricular enlargement with right ventricular hypertrophy; left atrium is enlarged. Vascularity of the lungs is increased.

TABLE I
Finding of Cardiac Catheterization in Patient at the Age of Six Months (January 1959)

Place of the Catheter	Pressure (mm. Hg)			O_2 (vol. %)	O_2 Capacity	O_2 Saturation
	Systolic	Diastolic	Mean			
SVC	...	...	...	8.9	...	61
IVC	...	...	...	10.0	...	69
RA	a=7 v=5	...	4	9.2	14.4	63
RV	82	8	27	9.0	...	62
PA	20	7	13	10.6	...	73
PCV	...	...	6	...	...	...
Coronary sinus	...	...	...	7.2	...	49
Femoral artery	...	...	...	13.3	...	91

NOTE: Blood pressure by cuff method 70/50 mm. Hg. SVC = superior vena cava; IVC = inferior vena cava; RA = right atrium; RV = right ventricle; PA = pulmonary artery; PCV = pulmonary capillary venous.

correction was to be performed when the child was older. She was discharged from the hospital in February 1959. One month later she was admitted again because of an infection of the upper respiratory tract and urinary tract. The clinical picture had not changed during this interval although the heart showed a slight reduction in size (relative heart volume, 420 cc.). This process had become more marked at the time of the third admission two months later, when the relative heart volume had diminished to 340 cc. The heart was now only moderatly enlarged. It was noticed that the expansion of the left atrium and the degree of pulmonary vascularity were less marked, indicating a reduction in flow through the lungs and consequently a diminishing left to right shunt. Clinically, the child now showed clearer signs of right

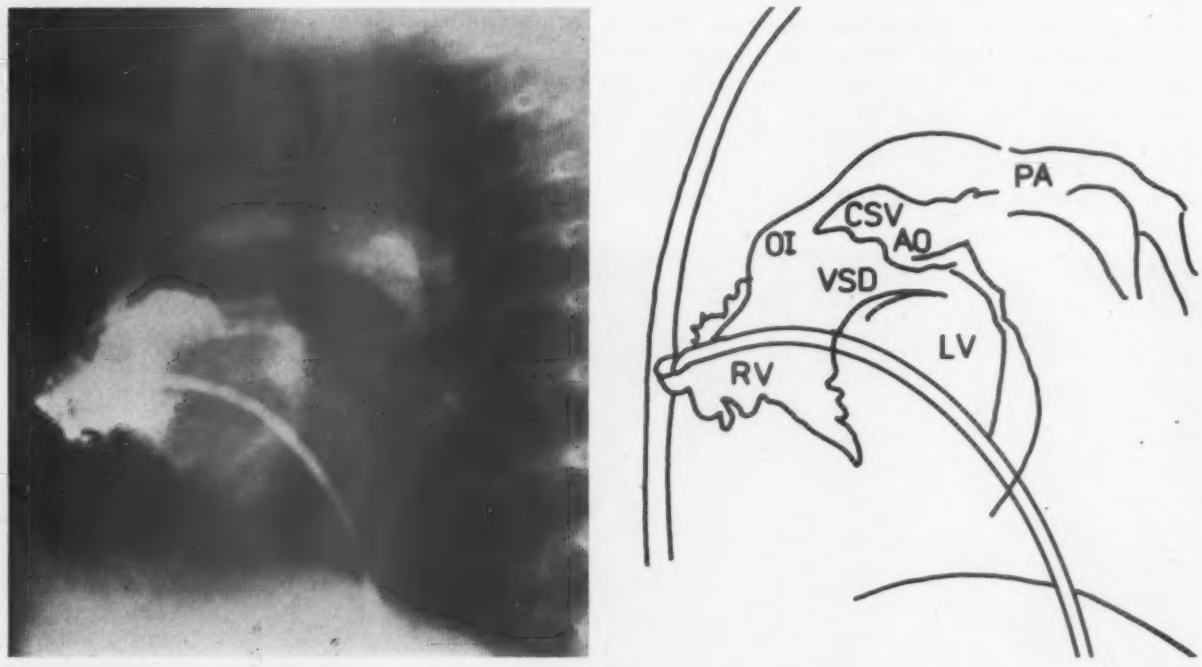

FIG. 3. Angiocardiogram (lateral view) and drawing during ventricular systole. The contrast medium injected into the right ventricle (RV) outlines the ventricular septal defect (VSD) and partially escapes into the left ventricle (LV). The septal defect is located behind and below the crista supraventricularis (CSV) and in its superior aspect is bordered by the under surface of the aortic cusps (AO). There is no intervening septal tissue below the anterior part of the right aortic cusp. This indicates that the septal defect extends anterior to the papillary muscle of the conus. In this phase, the infundibulum and particularly the ostium infundibuli (OI) are contracted. PA = pulmonary artery.

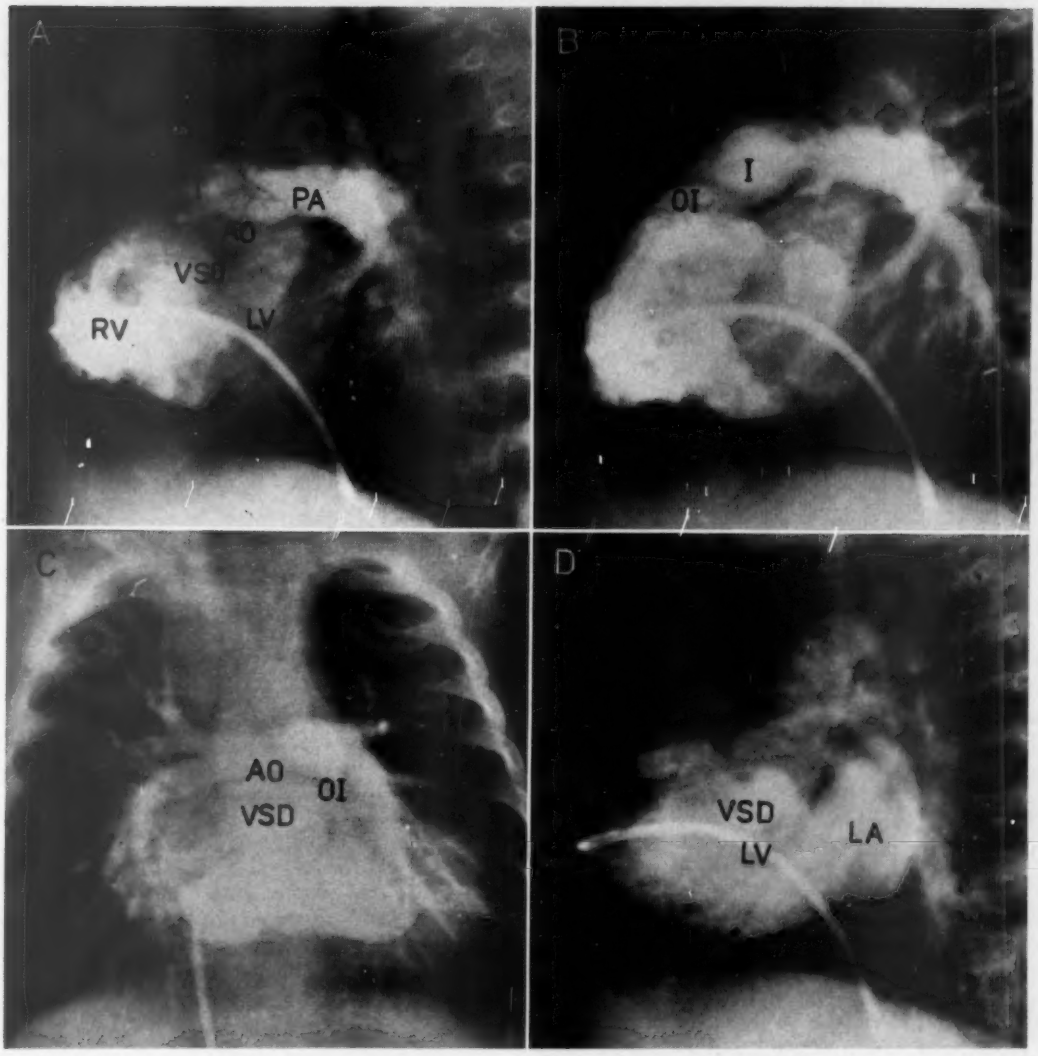

FIG. 4. Angiocardiogram. *A*, lateral view during early diastole (probably isometric relaxation phase). The right aortic valve (AO) faces the ventricular septal defect (VSD). The pulmonary valves are also seen (to the left of PA). Contraction of infundibulum (I) persisted in this phase. RV = right ventricle; LV = left ventricle. *B*, lateral view. In full diastole (presystolic phase) a slight constriction is evident in the ostium infundibuli (OI). The right ventricle including its infundibulum (I) is moderately dilated. Atrial systolic impact has opened the pulmonary valves. The pulmonary artery has a typical dorsal course. *C*, A-P view. Early ventricular systole. Slight distortion of the ostium infundibuli (OI) with abnormal course of the parietal and septal bands of the crista supraventricularis. The pulmonary trunk is superimposed on the infundibulum in this view. Slight dilatation of the pulmonary artery and its branches. The ventricular septal defect (VSD) faces the aortic root (AO). *D*, lateral view. Late diastole. The left atrium (LA) is dilated as is the left ventricle (LV). A left to right shunt is transmitted through the ventricular septal defect (VSD). Because of the shunt the subinfundibular tract of the right ventricle is demonstrated anew.

to left shunt. She was pale and a slight cyanosis was present even at rest.

The patient was admitted to the hospital for the third time because of repeated infections of the urinary tract. During a cystoscopic examination cardiac standstill occurred. Immediate attempts at resuscitation by thoracotomy and heart massage were followed by prompt restoration of rhythm.

Intravenous urography demonstrated a right-sided ectopic ureter and a heminephrectomy was performed. The specimen showed renal dysplasia and pyelonephritis. The postoperative course was uneventful. Following discharge from the hospital on June 25, 1959 she continued on a progressively downhill course until the final hospital admission on August 11, 1959 at the age of twelve months. The mother reported that during this last interval the child's general condition had deteriorated and re-

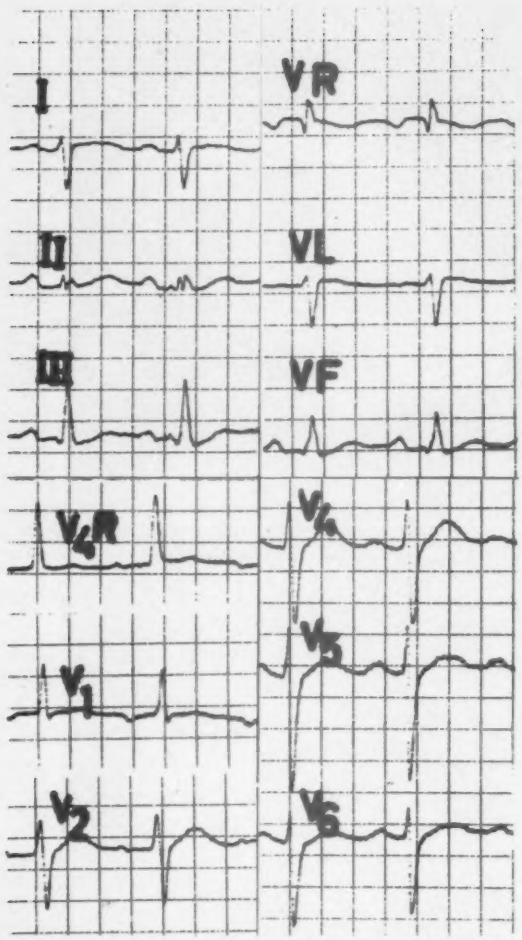

FIG. 5. Electrocardiogram during the last admission at the age of twelve months. Note the more pronounced right axis deviation (+110°) as compared to Figure 1 and the clockwise rotation of the heart with the deeper S wave in V_6.

peated attacks of cyanosis and unconsciousness had occurred.

Final Hospital Admission: Significant clinical and laboratory changes were noticed on this admission. The child had definite cyanosis with clubbing of the fingers. She had a somewhat rapid respiratory rate (about 40 per minute). The cardiac findings had not changed appreciably and no signs of heart failure were present. A rise in hemoglobin to 16.5 gm. per 100 ml. was noticed in comparison with a previous value of 11.2 gm. The *electrocardiogram* (Fig. 5) showed that the electrical axis had shifted to the right (+110°) and the pattern of right ventricular hypertrophy was more pronounced with a flattening of the T wave in the right precordial leads and a deeper S wave in V_6. The *roentgen examination* of the heart revealed a further decrease in relative heart size (Fig. 6). It had now diminished from the original 450 to 290 cc. The left atrium did not show any significant enlargement. The vascularity of the lungs was regarded as normal or slightly reduced.

Because of the patient's age and her serious general condition, an operation using extracorporeal circulation was believed a great risk. For this reason, a shunt operation was decided upon and the patient was transferred to the surgical department. She contracted a new respiratory infection as well as an infection of the intestinal tract and her general condition deteriorated. In spite of intensive medical treatment she never improved. Twenty-four hours before death she showed signs of cerebral anoxia with repeated attacks of convulsions and unconsciousness. She died on August 31, 1959 at the age of thirteen months.

Postmortem Examination

The autopsy was performed thirty-seven hours after death. The body was that of a well developed, poorly nourished female child weighing 8 kg. and measuring 78 cm. Cyanosis was prominent over the lips and nail beds; clubbing of the fingers and toes was moderate. The skin was pale and no edema was present. The anterior fontanel was open to the size of a fingertip. The findings of main interest were limited to the cardiovascular system.

Heart: Before dissection, 10 per cent formalin was injected into the coronary arteries until the pulmonary trunk was filled. The heart-lung specimen was then immersed in a 10 per cent formalin solution for twenty-four hours. The heart was enlarged, the fixed organ weighing 94 gm. (normal, 44 gm.) The superior and inferior venae cavae and the coronary sinus opened normally into the right atrium which was of normal size and shape. The foramen ovale was closed. The tricuspid valve was normal with three well formed leaflets. The right ventricle was slightly dilated and the wall was markedly hypertrophic, measuring 9 mm. in thickness. There was a defect in the upper portion of the ventricular septum located anterior to the papillary muscle of the conus (Fig. 7). The papillary muscle of the conus inserted onto the posterior third of the lower border of the defect. The root of the aorta was dextroposed, the entire right and part of the posterior cusps of the semilunar valve being located to the right and anterior to the ventricular septum.

The crista supraventricularis displayed the abnormal location characteristic of the tetralogy of Fallot. Thus, the parietal band was rotated and displaced anteriorly and superiorly with moderate anterior displacement of the septal band. In addition, the distorted ostium infundibuli was stenosed by prominent fibrous ridges deposited all around its wall (Fig. 7E). The narrow ostium had a triangular outline measuring 4 by 4 by 6 mm. It opened into a large infundibular chamber or "third ventricle," which in turn emptied into the pulmonary trunk through a normal valvular ostium. The pulmonary vascular tree was normal on gross examination, and the two pair of pulmonary veins emptied into the left atrium which was of usual size and shape. The

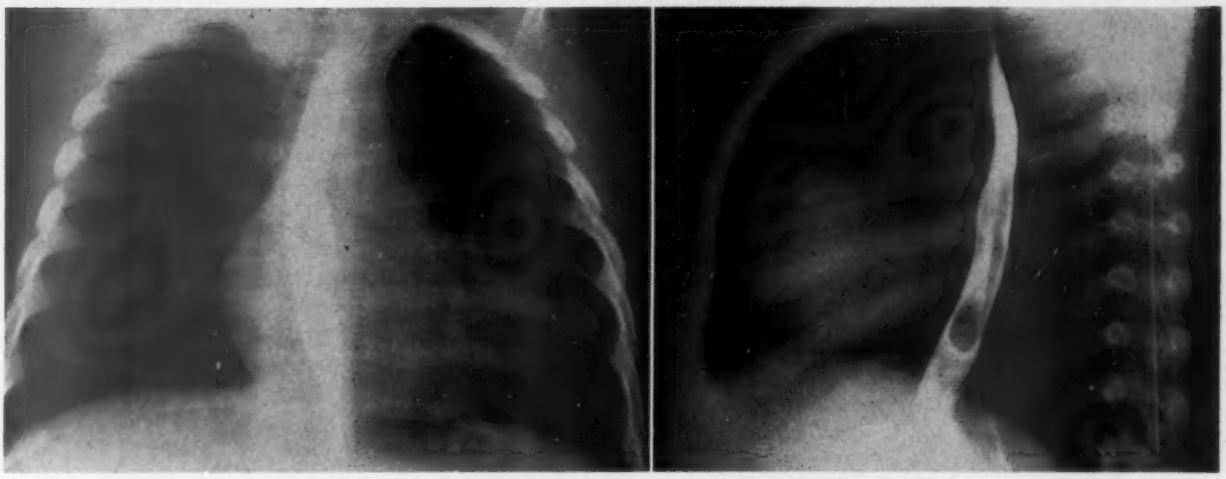

FIG. 6. Roentgenograms at age twelve months in P-A and lateral views. Great reduction of heart volume as compared to Figure 2. The relative heart volume now measures 290 cc. No dilatation of the left atrium. Vascularity of the lungs is somewhat scanty.

mitral valve had normal leaflets and papillary muscles. The left ventricle was somewhat enlarged but of unremarkable configuration, its wall measuring 8 mm. in thickness. The aorta was of usual width with normal main branches and a left-sided aortic arch with closed ductus arteriosus. In the anterior wall of the descending thoracic aorta two dilated but equal bronchial arteries with slightly widened openings were found.

The lungs were slightly atelectatic but no congestion or edema was present. Gross examination of the abdominal viscera revealed moderate congestion. The right kidney was scarred in the upper pole where the heminephrectomy had been performed. The remaining part of this kidney was congested but otherwise within normal limits. The ureter was somewhat dilated but there were no signs of active disease in any part of the urinary tract. Congestion of the meningeal vessels and rather prominent cerebral edema were present but no further intracranial lesions could be found.

Microscopic Examinations: The ostium infundibuli and neighboring structures were removed en bloc after fixation of the heart. The block was embedded in paraffin and serially sectioned in a plane parallel to the outflow tract of the right ventricle. Every tenth section was collected and stained according to Verhoeff's method for elastic tissue counterstained with van Gieson's stain for connective tissue.

The entire circumference of the ostium was lined with endothelium covering a thick layer of cellular connective tissue rich in capillaries (Fig. 8). This tissue contained fibroblasts and occasional lymphocytes, but no mineral salt deposits or hemosiderin. A fine reticular stroma of collagenous fibers was encountered interspersed with irregular streaks of elastic fibers. The latter were noted in the subendothelium and adjacent to the underlying myocardium, in a position parallel to the endothelial surface and never perpendicular to it. In the center of the fibrous tissue there were areas with degenerative hyaline changes of the collagen. In routine lung sections and in those stained for elastic fibers, no changes could be found except for very scanty atelectatic areas. The branches of the pulmonary artery displayed no abnormal feature.

Pathologic Diagnosis: Tetralogy of Fallot, characterized by stenosis of the ostium infundibuli of the right ventricle due both to displacement of the muscular bands of the crista supraventricularis and to superimposed subendocardial fibrosis; ventricular septal defect located anterior to the papillary muscle of the conus; marked cerebral edema.

COMMENTS

It has been repeatedly demonstrated that in ventricular septal defect with pulmonary stenosis there may be a left to right shunt, sometimes quite large.[1-9] The functional status of such patients depends mainly on the degree of pulmonary stenosis and the pressure gradient across the ventricular septal defect. Both these features may vary considerably during the lifespan of each patient. Thus, the hemodynamic data obtained at the time of cardiac catheterization are not enough to permit accurate prediction of the course of the disease.

An appreciation of those factors regulating the changing manifestations of the particular heart lesion is obtained from repeated clinical evaluations and from precise knowledge of the anatomic arrangement underlying the functional features. The value of such anatomic information is made evident by recalling that

there are several types of ventricular septal defect, each having a different and characteristic position and relationship to right ventricular structures. In addition, pulmonary stenosis may be valvular, infundibular or both. Because of such great anatomic variations one cannot assume that a valvular pulmonary stenosis with a ventricular septal defect located posterior to the papillary muscle of the conus will have the same clinical behavior and surgical prognosis as infundibular stenosis with a ventricular septal defect extending anterior to the papillary muscle of the conus.

The changing clinical pattern in patients with ventricular septal defect in whom obstruction of the outflow tract of the right ventricle gradually develops has been noted by several authors.[1–5] The frequency of this secondary change is greater than previously suspected. This is due to the fact that today

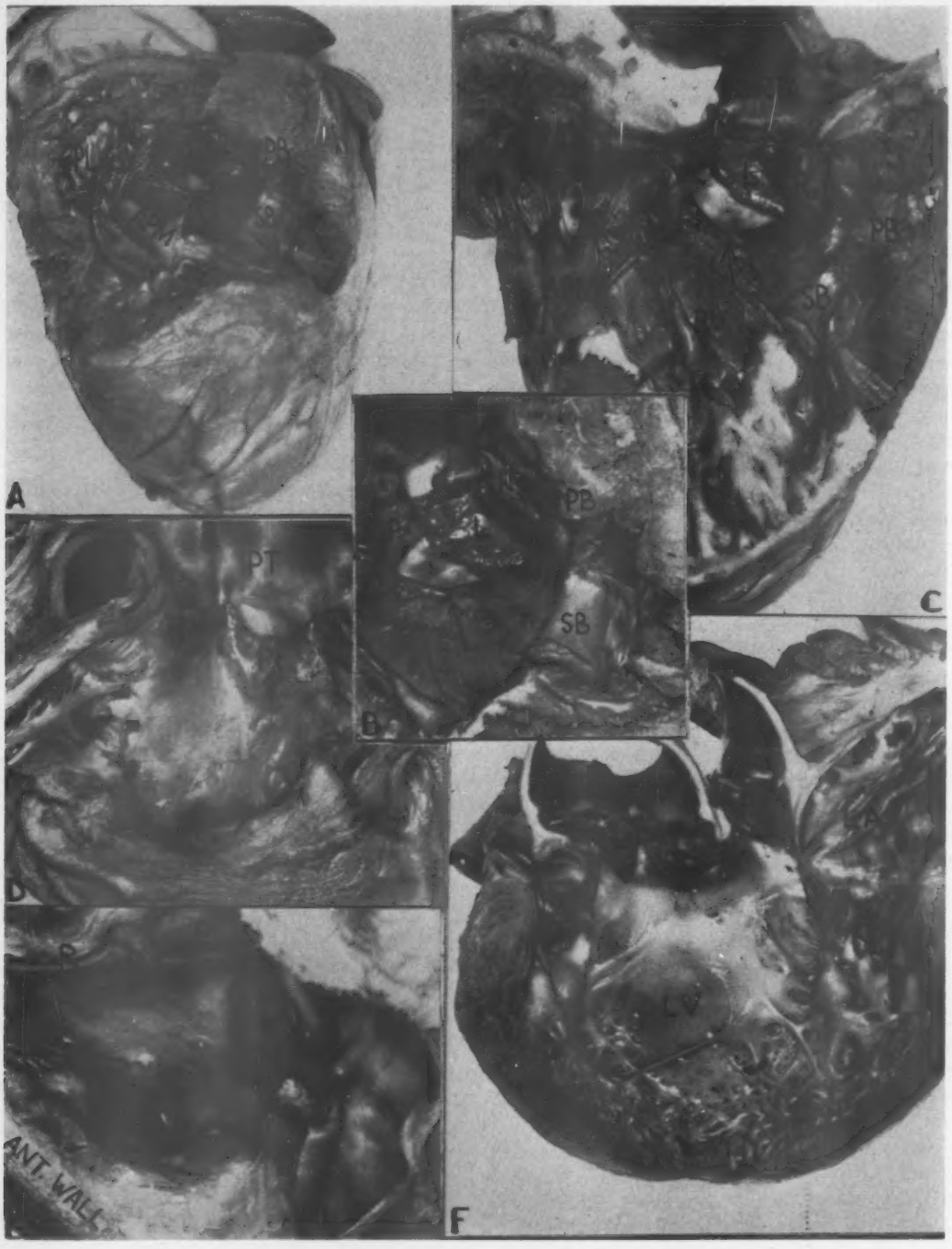

FIG. 7. *Legend on facing page.*

an increasing number of patients with congenital heart disease are being carefully followed from birth. The basis for the secondary cardiac change becomes apparent only when adequate anatomic information is available; this has not been presented in any of the previously reported cases.

In the tetralogy of Fallot the ventricular septal defect is located between a posteriorly displaced papillary muscle of the conus and a crista supraventricularis which is rotated and displaced anteriorly and superiorly. In such hearts the size of the ostium infundibuli may be very small at birth or it may be wide enough to permit increased flow of blood to the lungs with no right to left shunt. In these cases there may or may not be a demonstrable pressure gradient across the right ventricular infundibulum.

In the patient reported here the available evidence indicates that at the time of the initial examination at the age of four months there was only a moderate obstruction at the right ventricular outflow tract. This permitted a large left to right shunt to exist through the ventricular septal defect, as was demonstrated by the radiologic examination. Cardiac catheterization performed two months later showed clear signs of obstruction at the ostium infundibuli, equilibrated ventricular pressures and a bidirectional shunt. In addition, the angiocardiogram gave a precise anatomic description of the underlying malformation.

In the subsequent course over a period of six months, clinical data indicated a progressive obstruction of the outflow tract of the right ventricle leading to the production of a predominantly right to left shunt with paroxysmal and later almost permanent cyanosis. This striking clinical and hemodynamic change was paralleled by a continuous reduction in the size of the heart as well as in the vascularity of the lungs.

Postmortem examination confirmed the relationships demonstrated by angiocardiography between the ventricular septal defect and the papillary muscle of the conus. The abnormally located muscular bands of the crista supraventricularis were covered at the ostium infundibuli by thick ridges of fibrous tissue. The character

FIG. 7. Views of the heart at autopsy. *A*, the right and most of the posterior wall of the right ventricular inflow chamber have been removed, preserving the insertion of the anterior papillary muscle (APM). The chamber is viewed from the apex upwards, after posteriorly retracting the body of the APM. The position of the papillary muscle of the conus is indicated by the arrow as in illustrations B and C. When the right ventricular chamber is viewed in this manner the ventricular surface of the anterior tricuspid leaflet (AL) can be considered to be a plane continuing upwards into the aortic root, in close relationship to the posterior aortic cusp (P). The under surface of the right aortic cusp (R) hangs entirely to the right of the ventricular septum. The papillary muscle of the conus inserts onto the posterior third of the lower border of the ventricular septal defect. Of main interest is the position of the muscle bands of the crista supraventricularis. The parietal band (PB) is rotated and displaced anteriorly away from the tricuspid ring. The upper portion of the septal band (SB) is also displaced anteriorly and superiorly, but its lower portion reaches the base of the anterior papillary muscle as a normally located "moderator band." OI = ostium infundibuli; PL = posterior tricuspid leaflet. *B*, close-up view of the area of the ventricular septal defect and the ostium infundibuli. Notice the relationship of the displaced crista to the papillary muscle of the conus and the ventricular septal defect. Along the borders of the ostium infundibuli there are prominent ridges of fibrous tissue causing the orifice to have a triangular configuration. The broken line indicates the plane along which the ostium infundibuli was serially sectioned, demonstrating the microscopic features illustrated in Figure 8A. *C*, the right ventricular inflow chamber has been opened by sectioning along the outflow tract leading to the aorta, and retracting the anterior papillary muscle posteriorly. The ostium infundibuli and the pulmonary outflow tract have not been opened. The distribution of the valves and the muscle bundles in the right ventricle is best seen in this view; it gives a distorted but schematic representation of the malformation which is characteristic and defines the tetralogy of Fallot, even in the absence of hemodynamic significant obstruction to pulmonary flow. This patient had a pronounced obstuction at the level of the ostium infundibuli in connection with the ridges of fibrous tissue deposited upon it. *D*, above the ostium infundibuli the pulmonary outflow tract dilates to form a prominent "third ventricle," and this chamber is opened and seen from the front. PT = pulmonary trunk; R = right, P = posterior, and L = left pulmonary cusps, which are normal in size and configuration. *E*, looking down into the chamber of the "third ventricle," the ostium infundibuli is seen as an irregular opening surrounded by fibrous tissue. Notice the position of the muscle bundles of the parietal (PB) and septal (SB) bands of the crista. If the fibrous tissue were not present, the ostium infundibuli would have the size and configuration indicated by the interrupted line and its borders would then be purely muscular. *F*, the left side of the heart opened in the classic manner. The left ventricular chamber is large in relation to the large pulmonary flow present during most of the patient's life. LA = left atrium; LV = left ventricle.

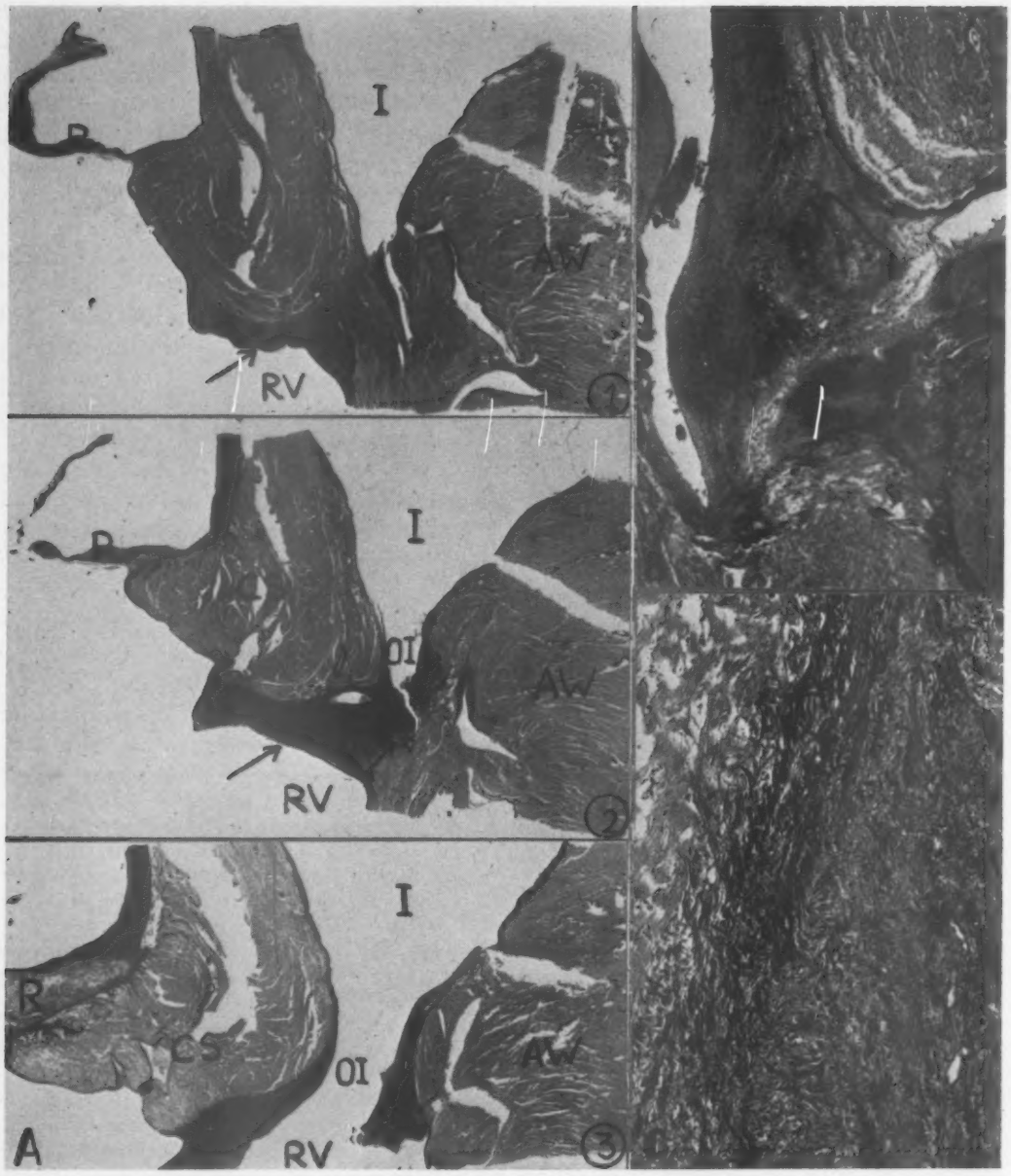

FIG. 8. Photomicrographs of heart. *A*, a sequence of sections through the infundibular region parallel to the outflow tract, about 1.5 mm. apart (planes of sections indicated by broken line in Fig. 7B). R = right aortic cusp; CS = crista supraventricularis; RV = right ventricle; OI = ostium infundibuli, I = infundibulum ("third ventricle"); AW = anterior wall. (Verhoeff-van Gieson stain; original magnification ×3.) *1.* Section through myocardium posterior to the ostium infundibuli and including the subendocardial fibrosis (arrow) of the lower portion of the ostium infundibuli. *2.* Tangential section of the inner layer of the wall of the ostium infundibuli showing the prominent fibrosis (arrow) extending along the border of the ostium. *3.* Section through the ostium infundibuli close to its midline showing the lumen to be narrowed by the subendocardial fibrous tissue. *B*, tangential section of the inner layer of the wall of the ostium infundibuli, (same area as in A2). The cellular ridge of fibrous tissue, rich in capillaries, is seen in the center, separated from the normal myocardium by thin streaks of elastic tissue. (Verhoeff-van Gieson stain; original magnification ×25). *C*, high power view of the subendocardial fibrous tissue, separated from the myocardium by elastic tissue. (Verhoeff-van Gieson stain; original magnification ×100.)

and distribution of this subendocardial fibrosis indicated that its process of formation was of an acquired and progressive nature, probably caused by the traumatic action of blood streaming across the displaced muscular trabeculae. A stiffening and subsequent narrowing of the ostium infundibuli resulted in the progressive obstruction to pulmonary blood flow, leading

to the successive alteration of hemodynamics outlined above.

Thus, the case reported herein explains the findings in previous studies[2-4] which suggested that the basis for the changing clinical pattern in some patients with ventricular septal defect is the gradual development of an infundibular stenosis. In our patient this process was associated with a progressive narrowing of the ostium infundibuli due to traumatic subendocardial fibrosis developing on the displaced bands of the crista supraventricularis. The characteristic anatomic arrangement within the malformed heart can be outlined by means of selective angiocardiography before the hemodynamic consequences of such a pathologic change become clinically apparent. In this manner, valuable information is added toward understanding the natural disease course of patients who, if not treated, ultimately manifest the picture of a classic tetralogy of Fallot which was previously absent.

Furthermore, this case emphasizes the concept that the anatomic relationship of the ventricular septal defect to right ventricular structures seems to be the best way of defining the malformation known as "tetralogy of Fallot." It is not possible and certainly would not be rewarding to attempt a hemodynamic definition which would apply to the different conditions present throughout the lifespan of all patients dying with "ventricular septal defect and pulmonary stenosis with right to left shunt and decreased pulmonary flow."

Summary

A four month old girl revealed clinical and roentgenologic signs of a ventricular septal defect with a left to right shunt and presumably moderate infundibular stenosis. The course of the disease was followed at almost regular monthly intervals by clinical and roentgenologic examinations until the death of the patient nine months later. Investigation by heart catheterization and selective angiocardiography at the age of six months disclosed a pressure in the right ventricle equal to the systemic, an infundibular stenosis and a bidirectional shunt through a ventricular septal defect located anterior to the papillary muscle of the conus.

The subsequent clinical course was dominated by transient and eventually permanent cyanosis due to an increasing right to left shunt. This was paralleled by diminished vascularity of the lungs, reduction in heart size and disappearance of a previous dilatation of the left atrium.

Autopsy confirmed the findings made at angiocardiography and in addition revealed subendocardial fibroelastic thickening on the moderately displaced crista supraventricularis. This fibrosis was considered to be due to the traumatic action of the blood flowing across the bands and could account for the gradually increasing obstruction of the infundibulum of the right ventricle in this and other cases with a similar clinical history.

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Bacterial Endocarditis Due to Salmonella Typhimurium*

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SALMONELLA ORGANISMS are found in the intestinal tract of man and animals, both wild and domestic. They can be isolated from all parts of the world. Over 200 serologic varieties have been identified on the basis of "O" and "H" antigens. They may produce a typhoid fever-like disease, a food poisoning syndrome, a septicemia or localized pyogenic infections. Bacterial endocarditis caused by a Salmonella organism is extremely rare. The following is a report of a case due to Salmonella typhimurium.

CASE REPORT

A forty-seven year old white female nurse was admitted to the hospital on May 14, 1956. The diagnosis on admission was chronic schizophrenic reaction, paranoid type, manifested by delusions, auditory hallucinations, destructiveness, writing abusive letters, lack of insight and inappropriate and flattened affect. She served in the U. S. Army from March 15, 1941, to July 27, 1942, and was retired because of mental illness. While in the service her joints swelled and a tonsillectomy was performed. She was told she had a "mild heart condition." About three years prior to admission easy fatigability, occasional shortness of breath and ankle swelling developed. For the past year she had dizzy spells and two-pillow orthopnea. She thought she might have been given digitalis in the past.

Physical examination revealed a tall asthenic white woman in no distress. A malar flush was present and she appeared slightly breathless; blood pressure was 104/80 mm. Hg, temperature 98.6°F., pulse 144 per minute, and respiration 22 per minute. The heart was moderately enlarged but no precordial pulsations were visible. A diastolic thrill was present at the apex. Auscultation revealed a diastolic rumble at the apex with an opening snap of the mitral valve. Along the left sternal border there was a grade 2 diastolic diminuendo murmur and P_2 was accentuated. Atrial fibrillation was present. The liver was palpable four fingerbreadths below the costal margin. There were spider varicosities on the legs and some edema of the feet.

Laboratory Examinations: The hemogram showed a normal white count and differential, a hemoglobin of 12.7 gm. per cent and a sedimentation rate of 19 mm. per hour. The VDRL test was negative. Urinalysis was within normal limits. Nonprotein nitrogen and fasting blood sugar were normal. The antistreptolysin 0 titer was 166 Todd units. The vital capacity was 3 L. A roentgenogram of the chest showed a vertical heart which was markedly enlarged. There was straightening of the left border of the heart. Both hilar vascular shadows were prominent and lung vascularity throughout was increased. On fluoroscopy the pulmonary vessels were active and there was displacement of the esophagus posteriorly and a little to the right. An electrocardiogram showed atrial fibrillation with a rapid ventricular response.

Clinical Course: She was digitalized with digitoxin and maintained with digitalis leaf. The signs of congestive failure disappeared. The atrial fibrillation persisted but the ventricular rate was slowed. In addition she received promazine, reserpine and chlorpromazine as needed for her mental state. On June 21, 1956 she experienced severe precordial pain lasting for three minutes with no new physical findings.

The terminal illness began on February 5, 1957 with temperature elevation. She complained of nausea, generalized aches, chilly sensations, weakness, and nonproductive cough. She said she had had a hamburger the night before. Hamburgers were served to all the other patients; none complained of the meat being spoiled or of getting sick from eating it. Soon thereafter a frontal headache and fever developed. The only new physical finding was a palpable spleen. Her rectal temperature was 104.8°F. and by the following day had risen to 106.8° (Fig. 1).

Seven blood cultures were taken, one on February 5, three on February 6, and three on February 7, 1957. All were positive for Salmonella group B.

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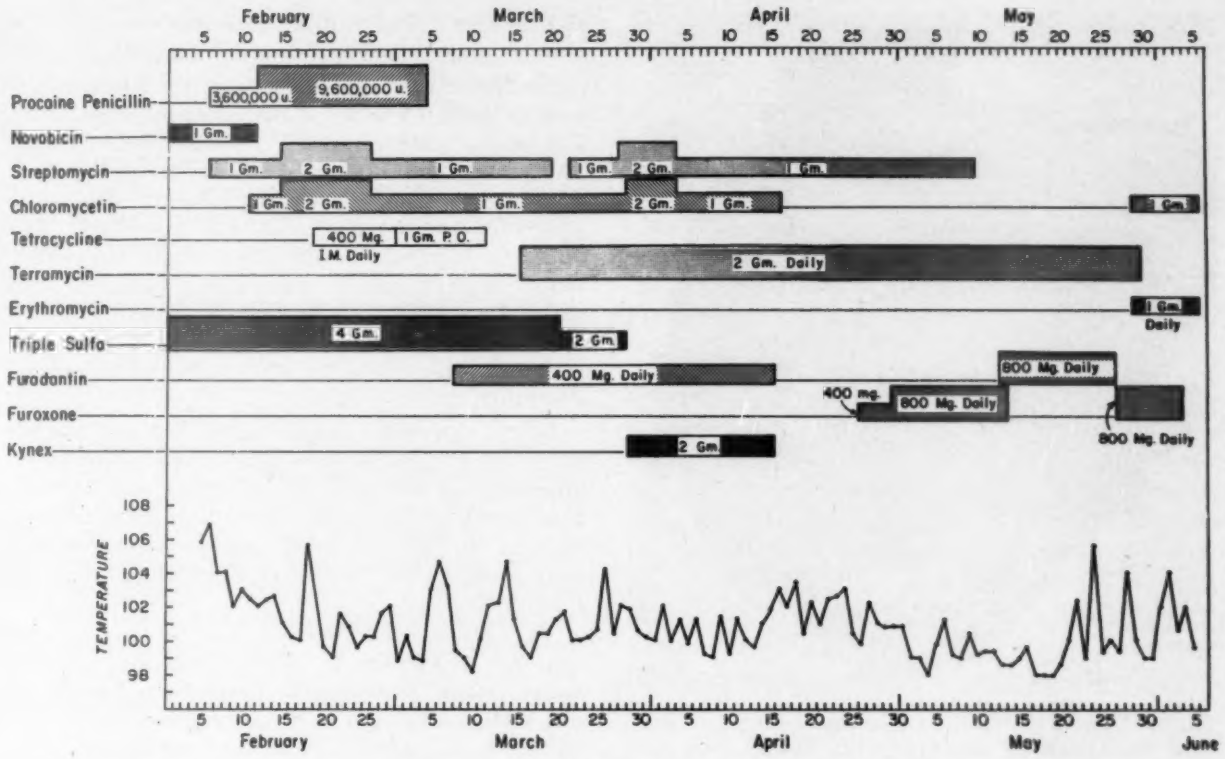

FIG. 1. Temperature curve and antimicrobial agents used in therapy.

This organism was further studied at the Walter Reed Army Institute of Research, Washington, D. C. and identified as Salmonella typhimurium. The antigenic analysis was 0 group antigens: 1, 4, 5, 12; flagellar or H antigens: i; 1, 2. She was immediately given penicillin. Many other antimicrobial agents were added (Fig. 1). Sensitivity studies on the original cultures and subcultures showed the organism to be sensitive to nitrofurantoin, streptomycin, and chloramphenicol. It was slightly sensitive to Terramycin and tetracycline. It was resistant to penicillin, Aureomycin, erythromycin, bacitracin, polymyxin and the sulfonamides. Agglutinations by the patient's serum showed a negative reaction to paratyphoid A and B while the typhoid H and O was positive 1 : 20. Eleven additional cultures, the final one on April 15, 1957, were negative.

A hemogram on February 5, 1957 revealed a white count of 5,850 with 77 per cent neutrophils, a hemoglobin of 14.2 gm. per cent, a hematocrit of 43 and a sedimentation rate of 25 mm. per hour. A roentgenogram of the chest on February 6, 1957 revealed some increase in the vascularity of the lungs and increase in the cardiac size. There was slight elevation of the right interlobar septum. The sedimentation remained consistently elevated and the C reactive protein showed a 4+ reaction. The antistreptolysin 0 titer remained the same. There was a gradual decline in the hemoglobin and by April 16, 1957 it was 9.8 gm. Blood transfusions (three) begun at this time caused a gradual rise. The white count on June 3, 1957 showed a rise to 11,500 with 76 per cent neutrophils. Serial x-rays revealed progressive enlargement of the heart, increased congestion of the lungs and suggestive enlargement of the liver and spleen. Repeat electrocardiograms were unchanged.

The initial high temperatures subsided slowly but she continued to have a low grade fever with intermittent spikes. There was no definite response to any of the various antibiotics or to any combinations of the same. She progressively deteriorated although there were periods of temporary improvement. There was progressive weight loss and variable appetite. Spiking temperatures were associated with chills, nausea, weakness, malaise, dyspnea, pallor, cyanosis and profuse sweats. Puffiness of the ankles developed on March 20, 1957 and diarrhea on May 2, 1957. On May 16, 1957 she began to complain of pain and numbness in the left foot. The right lower extremity then became involved and numbness in the hands ensued. There were, in addition, tenderness of the calf muscles, coldness of the feet and a bilateral foot drop. She then complained of rectal pain, photophobia, distressing odors and blood-streaked sputum. The pain in the lower limb became unbearable and she manifested mental confusion, delirium, and difficulty in swallowing. Pulmonary edema developed and then a shocklike state with imperceptible pulse, subnormal temperature and a blood pressure of 70/50 mm. Hg. Frequent jerking movements occurred and respiration became labored. She died on June 5, 1957.

FIG. 2. View of the opened left atrium and mitral valve. Note the thrombus attached to the walls of the left atrium.

AUTOPSY FINDINGS*

Heart: The pericardium was diffusely, irregularly discolored red and red-purple and there were numerous fibrinous adhesions throughout. About 50 cc. of slightly cloudy yellow fluid was present. Each pleural cavity contained 300 cc. of yellow fluid. The heart weighed 620 gm. There were fibrinous adhesions over most of the epicardium, especially over the left atrium and ventricle. The left atrium was irregularly dark red, red-purple and gray-white externally. The right atrium and ventricle were moderately dilated, the myocardium was homogeneous. The tricuspid valve appeared normal. The chordae tendineae and papillary muscles were slightly thickened and the right ventricular myocardium was 0.4 cm. thick. The pulmonary valve and artery were unremarkable.

The greatest dimensions of the left atrium were 11.5 by 9.2 by 6.6 cm. Filling the greater portion of the lumen was a friable, dull mass of varying shades of red and gray adherent to all luminal surfaces (Fig. 2). The mass did not extend into the pulmonary veins or mitral orifice. An irregular channel was present between the vessels and the mitral valve outlet. The mitral valve was 3.4 cm. in circumference and its greatest dimensions were 1.5 by 0.3 cm. The mitral annulus was very firm but there were no verrucae. It did not have the consistency of calcified tissue. The mitral leaflets were very short, thick and resilient. The chordae tendineae were adherent to each other. The left ventricle was not dilated, the endocardium was smooth and the myocardium homogeneous. The myocardium was 0.6 cm. thick. The aortic valve was 6.2 cm. in circumference. The three cusps were minimally thickened but there was no alteration of the commissures. The aorta above the valve was smooth and glistening. The coronary arteries showed only occasional, white-yellow, slightly raised, firm intimal plaques. The aorta and some of the major arteries showed a few intimal plaques. These were more numerous in the abdominal segment of the aorta. One of the plaques was calcified.

Lungs: The right lung weighed 750 gm. and the left 740. The cut surfaces with the exception of the anterior were red, wet and glistening and dark red fluid could be expressed. Very firm dark areas up to 8 cm. in diameter which appeared wedge-shaped were present at the periphery, especially at the lower lobes.

The liver weighed 1490 gm. and was red, mottled tan, firm and glistening. The gallbladder contained many yellow, multifaceted, friable stones up to 0.9 cm. in dimension and 30 cc. of green viscid bile. The right *kidney* weighed 176 gm. and the left 164. The capsule was moderately adherent focally. The renal tissue in these areas was dull, depressed and somewhat nodular. The cortices were moderately hyperemic and 0.6 to 0.7 cm. thick. The adrenals were grossly unremarkable. The *spleen* weighed 430 gm. and the pulp was glistening, pale red and firm. The bone marrow was red-brown and glistening. The brain weighed 1,260 gm.; on fixation and section no gross abnormalities were noted.

Microscopic examination revealed the following: The epicardium was covered by fibrin and numerous granulocytes along with a few vascularized fibrous adhesions. The underlying tissue showed numerous granulocytes and hyperemia. The myocardium of the ventricles had enlarged muscle bundles and nuclei. The aortic valve had a slight increase in fibrocollagenous connective tissue in the annulus but the cusps were unremarkable. The mitral valve was similar in appearance but the leaflets were thickened by similar connective tissue in which there were several small endothelial lined spaces containing blood. Adjacent to this the connective tissue was slightly loose and free of leukocytes. The left atrial myocardium had numerous areas of fibrous tissue near the luminal surfaces. Within the lumen of the left atrium there was a mass of fibrin, blood elements and necrotic material (Fig. 2). The cut surface of this material was cultured and a gram-negative bacillus (Salmonella typhimurium) was obtained. The periphery of the mass was composed of dense fibrocollagenous connective tissue which merged with the endocardium, and fibrosis of the myocardium. The coronary vessels showed intimal hyalinized connective tissue but no luminal compromise or leukocytic exu-

* Autopsy was performed by Robert B. Klein, M.D., Cabarras Memorial Hospital, Concord, North Carolina.

date. The aorta showed minimal increase in hyalinized connective tissue. There was increase in the amount of elastic tissue in most of the major pulmonary arteries and within the pulmonary parenchyma.

The lungs showed numerous areas of hemorrhage in the alveoli and in some small bronchioles. Even more diffusely the alveoli were filled with amorphous, eosinophilic material with no leukocytes. These showed a tendency to obscure the alveolar enlargement, clubbing of alveolar spurs and focal interstitial fibrosis. No vascular thrombi were noted. The hepatic sinusoids were widened and filled with blood especially in the central aspects of the lobules. In these areas some liver cells had small intracytoplasmic vacuoles while others contained a small amount of coarsely granular yellow pigment. Cells at the periphery of the lobule and in the portal areas were unaltered. The kidneys showed small indiscrete scars with some mononuclear cells and occasionally a hyalinized glomerulus. In the pelvic walls could be found lymphocytes, plasma cells and eosinophilic granulocytes. The splenic pulp was slightly hyperemic. Examination of the brain and peripheral nerves showed no alterations.

Comments

A review of the literature by Stumpe and Barrody[1] for the years 1936 through 1950 revealed twenty-one reported cases of Salmonella endocarditis, all of which terminated fatally. From 1951 to 1956, seven additional cases of Salmonella endocarditis were reported.[1,2–4] Of this entire group of twenty-eight patients since 1936, only two survived.[3,5]

Other reports of Salmonella endocarditis with recovery do not appear valid; there was insufficient evidence in these cases to conclusively establish the diagnosis of endocarditis. Gouley and Israel[6] in 1934 reported a case of Salmonella suipestifer complicated by endocarditis with spontaneous recovery. The diagnosis of endocarditis was made on the development of "a mitral and aortic murmur" at the height of the fever and the persistence of the mitral murmur after recovery. Hines[7] reported a case of bacteremia due to Salmonella montevideo with a soft precordial systolic murmur before and after recovery. He suggested, without proof, that the murmur may have been due to endocarditis. In the cases of Salmonella endocarditis reported by Saphra[8] no information was furnished as to the source of the cases and detailed information about each case was lacking. No analysis of this group could be made. The remaining cases in the literature were analyzed and the incidence of the offending species of Salmonella was as follows:

Salmonella suipestifer (choleraesuis)[2,4,5,9–11]	8
Salmonella paratyphi B[12–14]	3
Salmonella typhimurium[15,16]	2
Salmonella sp. (type Minnesota)[17]	1
Salmonella sp. (type Fayed)[18]	1
Salmonella sp. (type Oranienburg)[1]	1
Salmonella typhi[19]	1
Salmonella sp. (type Sendai)[3]	1
Salmonella sp.[4]	1

Site of Endocarditis: An effort was made to determine the frequency of preexisting valvular disease and which valve or valves were most commonly involved. In only fifteen of all the cases reported could this be evaluated, the others having insufficient information. Of these fifteen, eleven had some form of preexisting valvular disease. Of the eleven, seven had rheumatic heart disease, five with mitral disease and two combined mitral and aortic disease; one had calcific aortic disease; two had a bicuspid aortic valve and one had syphilitic aortitis. The bacterial process involved one or both of the valves in the left side of the heart in ten of the eleven cases. In the remaining case there was involvement of the ventricular septum with perforation of the septum.

There were three other cases[4,9,10] in which the organism was revealed in a thrombus. In the first three cases[9] there was a sinus tract from the right atrium into the left ventricle with vegetation and thrombi at each end. In the second case[10] a thromus was attached to the apical surface of the mitral valve. In the third case[4] the organism was noted not only in a mural thrombus in the left ventricle but also in a myocardial scar secondary to an anterior myocardial infarct. In the present case report the thrombus with its offending organisms was attached firmly to all walls of the left atrium. The inability of the therapeutic agent to reach the organism is clearly illustrated by these four patients.

Treatment and Prognosis: The treatment of Salmonella endocarditis has thus far been unsatisfactory. Four patients[9,10,17] failed to respond to sulfonamides. One patient[17] was treated with sulfonamides in combination with streptomycin without apparent benefit. One received penicillin and streptomycin and one received penicillin, tetracycline and chloramphenicol without effect.[4] In three cases[1,2,15] in which chloramphenicol was used there was no detect-

able clinical response although *in vitro* studies showed the organism to be sensitive to the drug. In these same patients, penicillin in varying amounts was used prior to or in association with the chloramphenicol without apparent effect.

McFadzean and Chi-To[3] reported a case of Salmonella endocarditis with recovery. The diagnosis appeared reasonably established in that the patient had a combination of rigors, high fever, petechiae, a harsh aortic systolic murmur with a thrill and positive blood and marrow cultures. He was treated with penicillin and chloramphenicol. He became asymptomatic and afebrile seven days after beginning the penicillin therapy and three days after starting chloramphenicol. Boger[20] noted that the Salmonella typhosa organism could be killed with a penicillin dosage of 25 units per cc. *in vitro*. He suggested the use of this drug in combination with Benemid® in the treatment of typhoid fever rather than the use of chloramphenicol. Rich and St. Mary[5] reported a nonfatal case of Salmonella endocarditis in which the offending organism was S. choleraesuis. The patient was known to have rheumatic mitral valve disease. Treatment with a variety of antibiotics was without benefit. The patient then received polymyxin and penicillin for several weeks during which time he became afebrile.

Apparently there have been no other cures of Salmonella endocarditis regardless of the therapeutic agent. Our experience parallels that of the other authors in that the patient died despite intensive therapy with numerous antibiotics to which the organism was shown to be sensitive *in vitro*.

Summary

The case of a forty-one-year old white woman with fatal Salmonella endocarditis is presented. The occurrence of Salmonella endocarditis is rare with only twenty-eight cases reported from 1936 through 1959. In the majority of cases there was some form of pre-existing valvular disease. The results of therapy remain unsatisfactory with only two known survivors. One of the difficulties of therapy is illustrated by the present case report. After therapy was instituted blood cultures were consistently negative. *In vitro* studies revealed the organism to be sensitive to several therapeutic agents. Despite this, Salmonella typhimurium was readily cultured from the left atrial thrombus at autopsy. Inability of the therapeutic agent to reach the organism appears to be the major difficulty.

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Phasic Respiratory Paroxysmal Auricular Tachycardia*

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ONE OF THE FUNDAMENTAL features of paroxysmal tachycardia is the tendency to recurrent attacks, the onset of which is often related to well defined stimuli. These stimuli are, in general, of a reflex nature and may have their origin in extracardiac organic disorders but in most cases they are of a functional nature. Indeed, cases of paroxysmal tachycardia following emotional stress, dreams, changes in posture,[1] voluntary maneuvers[2] and even, paradoxically, vagus stimulation (Valsalva maneuver[2] or carotid sinus pressure[3]) are known. In exceptional instances normal physiologic phenomena such as the periodic alternation of respiratory phases are sufficient stimuli to induce paroxysmal tachycardia.

The first case of paroxysmal tachycardia related to normal phases of respiration was described by Leigh in 1950.[4] This was a benign but persistent case of paroxysmal auricular tachycardia related to the inspiratory phase; it was unaffected by digitalis and quinidine. Katz and Pick[5] later reported an electrocardiogram in which the relationship between anomaly of the rhythm and respiratory phase was clearly demonstrated. No other similar reports have been noted in the literature.

This report describes a case of phasic respiratory paroxysmal tachycardia in which the arrhythmia responded to treatment with digitalis and quinidine but recurred as soon as the treatment was discontinued. Moreover, in this case vagus stimulation occasionally elicited a paradoxical response.

CASE REPORT

C. M., a fifty-two year old woman, was first seen on September 19, 1959. Her past history was noncontributory except for mild rheumatoid arthritis of five years' duration and symptoms of menopause for two years. On the date of first examination she complained of dyspnea on exertion, fatigue and palpitation, at times accompanied by a fleeting sensation of choking or pounding in the chest. These symptoms had begun four months prior to the examination but they were not severe and the patient was able to continue her work. There was no history of paroxysmal nocturnal dyspnea and there were no symptoms of congestive heart failure.

Physical examination revealed a moderately obese woman essentially normal except for signs of rheumatoid arthritis and the abnormal cardiac rhythm. Blood pressure was 130/70 mm. Hg. Respiratory rate was 16 per minute. Pulse was 100 per minute and irregular. The precordium was quiet; the heart sounds were normal and the heart size was normal on physical examination and fluoroscopy.

The electrocardiogram (Fig. 1A and B) revealed a complex arrhythmia consisting of a series of short bursts of paroxysmal auricular tachycardia recurring in a phasic sequence; onset and termination were related to the beginning and end of inspiration. Each burst began with a premature complex and ended abruptly with a compensatory pause. The atrial rate during the paroxysm was 240 per minute; ventricular rate was slightly irregular and varied from 120 to 150 per minute (2:1 atrioventricular conduction). The ventricular complexes were normal. Between the runs of tachycardia normal sinus rhythm was present at a rate of 83 per minute.

The patient was given 0.5 mg. digoxin daily for six days and then increasing doses of quinidine from 0.2 gm. to 1 gm. daily. She was seen again fifteen days later, on October 5, 1959, and reported no symptoms except for slight gastric intolerance to quinidine. An electrocardiogram taken on that date (Fig. 1C) revealed a sinus rhythm with occasional auricular premature systoles. Various maneuvers, including forced inspiration, Valsalva maneuver and changes in posture, failed to elicit any ectopic rhythm.

On October 27, 1959 the patient reported recurrence of palpitation on exertion after she had been forced to discontinue therapy because of intolerance to quinidine. An electrocardiogram on this date (Fig. 2) again showed an arrhythmia consisting of short runs of tachycardia synchronous with inspira-

* From the Department of Medicine "Carati," Ospedale Maggiore di Niguarda, Milan, Italy.

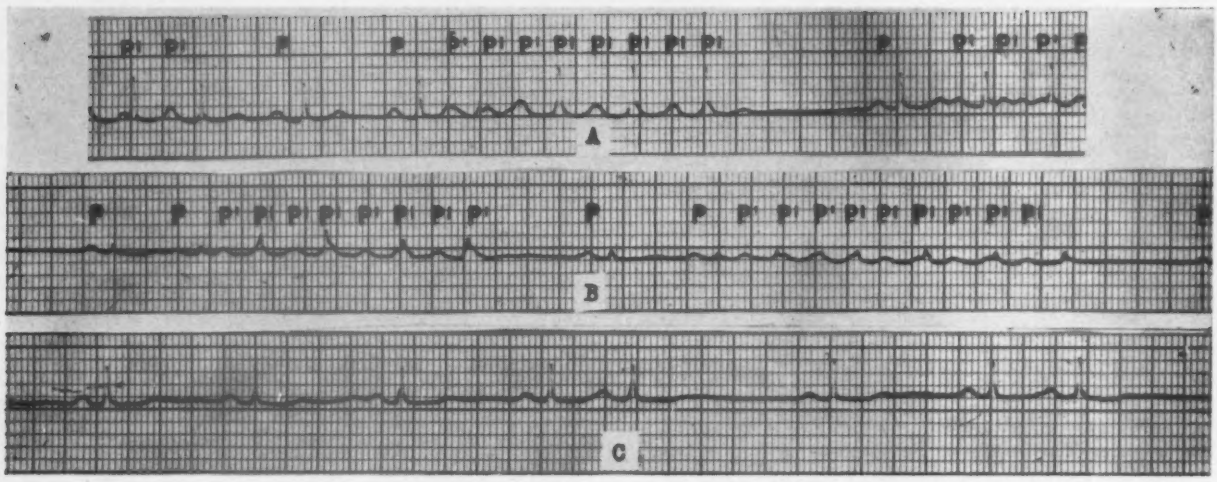

FIG. 1. *Records A and B* were taken on September 19, 1959 and are respectively lead II and aVF. Atrial complexes labeled P are sinus in origin, whereas those labeled P′ are ectopic. The sequence of paroxysmal auricular tachycardia related to normal inspiration is best seen in lead aVF. The record begins with a compensatory pause and two normal beats (expiration) followed by a short run of tachycardia which begins prematurely and ends abruptly (inspiration). This phenomenon recurs at each inspiration. *Record C* (lead II) was taken on October 5, 1959 after treatment with digitalis and quinidine. There is normal sinus rhythm with rare premature auricular systoles not influenced by respiratory maneuvers.

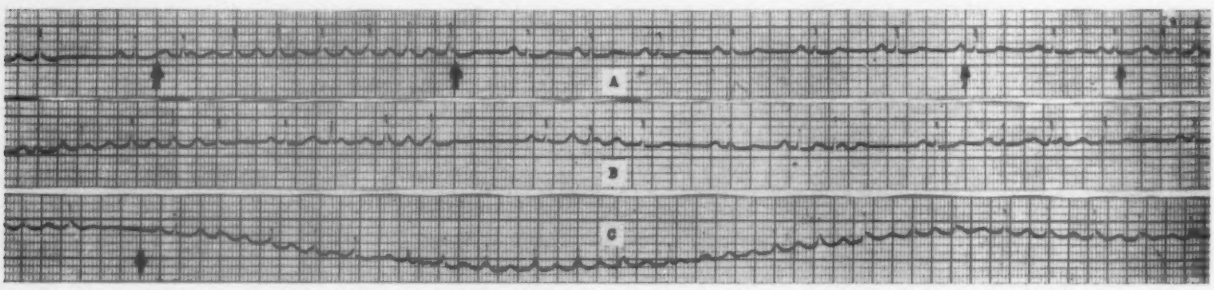

FIG. 2. The tracing (lead II) was taken on October 27, 1959 after all therapy was discontinued. *Record A:* a run of auricular tachycardia begins with a forced inspiration (1st arrow); normal sinus rhythm persists during breath-holding and expiration (2nd and 3rd arrows); the ectopic rhythm recurs with the following normal inspiration. *Record B:* short bursts of paroxysmal auricular tachycardia related to voluntary rapid respiration. *Record C:* paroxysmal auricular tachycardia following carotid sinus pressure (arrow).

tion. Deep inspiration induced a longer run of tachycardia whereas during the breath-holding following forced inspiration normal sinus rhythm was maintained; paroxysmal tachycardia reappeared with normal inspiration (Fig. 2A). Voluntary rapid respiratory movements elicited shorter bursts of tachycardia (Fig. 2B). Eyeball pressure induced a transient suppression of the arrhythmia, whereas pressure on both carotid sinuses immediately precipitated a paroxysm of tachycardia which persisted throughout the maneuver (Fig. 2C).

The patient was given digoxin 0.5 mg. daily but the treatment was discontinued after one week. On November 14, 1959 the arrhythmia was unchanged.

COMMENTS

Both clinical and experimental observations have firmly established that stimuli arising in the respiratory tract can induce different forms of ectopic rhythms.[6] Even in healthy subjects the onset of sporadic ventricular extrasystoles may be observed during or after deep inspiration. Forced inspiration and other respiratory maneuvers may induce more complex forms of ectopic rhythms such as auricular fibrillation,[7] auricular flutter, paroxysmal nodal tachycardia, atrial and ventricular bigeminy and the Wolff-Parkinson-White syndrome.[8]

In the instance of paroxysmal auricular tachycardia, deep inspiration is a maneuver which is widely used to stop the paroxysm of tachycardia.[9] Nevertheless, cases have been reported in which such a maneuver has precipitated attacks of paroxysmal tachycardia.[2,10] The arrhythmia observed by us differs from these reported because of its synchronism with the normal respiratory phases. Con-

sequently, it must be assumed that the arrhythmia was induced by normal physiologic stimuli.

In phasic respiratory paroxysmal tachycardia the runs of tachycardia are directly related to inspiration so that short voluntary inspiratory movements elicit short bursts of tachycardia whereas during breath-holding the arrhythmia is absent. In these respects this arrhythmia resembles respiratory sinus arrhythmia. It demonstrates, as pointed out by Katz and Pick,[5] that on occasion the periodic variations of the tone of the autonomic nervous system related to the phases of respiration may influence impulse formation in ectopic foci. This probably happens because of an extreme sensitivity of the ectopic focus to otherwise ineffective stimuli. The mechanical factor of dilatation of the right atrium during inspiration may have enhanced this particular sensitivity to nervous stimuli.

Since, in our patient, no organic abnormalities were detectable we must assume that a functional basis for the onset of paroxysmal tachycardia was present in the atrial tissue and that this arrhythmia may be precipitated either by subminimal stimuli (increased sympathetic tone related to inspiration) or more intense stimuli (emotions, effort).

The onset of a longer attack of paroxysmal auricular tachycardia following carotid sinus pressure, a phenomenon noted by other observers,[3] is difficult to interpret but is more readily understandable since Scherf's[11] demonstration that intense vagus stimulation following topical application of aconitine in the dog's heart may lead to this ectopic rhythm.

Summary

A patient with phasic paroxysmal auricular tachycardia related to normal inspiration is described. This arrhythmia was fairly well tolerated, and responded to treatment with digitalis and quinidine but recurred as soon as the treatment was discontinued. Carotid sinus pressure occasionally elicited an attack of paroxysmal auricular tachycardia.

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Diagnostic Shelf

Double Apical Impulse as a Sign of Aortic Aneurysm*

ALDO A. LUISADA, M.D., F.A.C.C., *and* R. REICH, M.D.
Chicago, Illinois

THE CASE OF a sixty-three year old Negro woman with known heart disease since 1952 has been followed in the Dermatology Clinic for over ten years because of repeatedly positive serologic tests for syphilis (both in the blood and spinal fluid). She has been maintained with digitalis and diuretics since 1952.

In October 1959, she was admitted with congestive failure. X-ray films of the chest revealed a shadow in the upper left mediastinum. On fluoroscopy this shadow presented an expansile pulsation. Angiocardiography demonstrated a large saccular aneurysm of the ascending aorta with large clot formation.

The patient was readmitted in May 1960 with intractable heart failure and with symptoms of loss of weight, pain in the left side of the neck and shoulder and hoarseness.

PHYSICAL EXAMINATION

The patient appeared cachectic and was in acute distress because of pain and orthopnea. The neck veins were distended and showed poor pulsations. There was a marked enlargement of the heart both to the right and left. A bulge was noted in the upper left anterior aspect of the chest. The blood pressure was 130/60 mm. Hg; the pulse was 50 and irregular. *Heart:* The apical thrust was in the sixth left intercostal space at the anterior axillary line and seemed reduplicated. One impulse was felt in early systole and one in diastole. A grade 2 systolic murmur and a grade 3 diastolic murmur were audible at Erb's point, the former radiating toward the neck, the latter toward the xiphoid process. The radial arterial pulses were present and equal. There was a very large and tender liver and a positive hepatojugular reflux. There was no pedal edema.

The diagnosis was *syphilitic aortitis, aortic insufficiency and aneurysm of the thoracic aorta.*

LABORATORY DATA

The *blood count* was: hemoglobin, 10.5 gm. per 100 ml.; red blood cells, 3.6 million per cu. mm.; hematocrit, 36.5 per cent; white blood cells 6,000 per cu. mm. *Serology* revealed VDRL, 3+, 4+; Wassermann 3+, 4+. *Urinalysis* revealed albumin 1+, occasional hyaline casts. *Blood chemistry* showed total protein 7.2 gm., albumin 2.7 gm., globulin 4.5 gm., blood urea nitrogen 16 mg., glucose 106 mg., cholesterol 179 mg., bromsulfalein, 58 per cent.

GRAPHIC STUDIES

Electrocardiogram: The tracing showed atrial fibrillation and left ventricular hypertrophy and strain.

Phonocardiogram: A diamond-shaped systolic murmur of moderate amplitude was recorded over the base. An early diastolic murmur in decrescendo was present at Erb's point with downward transmission (Fig. 1, upper tracing).

Low Frequency Tracing of the Apex: A very unusual type of tracing was obtained (Fig. 1, middle tracing). A sharp, peaked, rapid, positive thrust occurred in early systole. This is the "apical thrust." Its sudden rise and rapid collapse is similar to that noted by French cardiologists of the past century in aortic insufficiency, the "choc en dôme." However, following the second sound there was a rapid rise with a further slower rise which culminated

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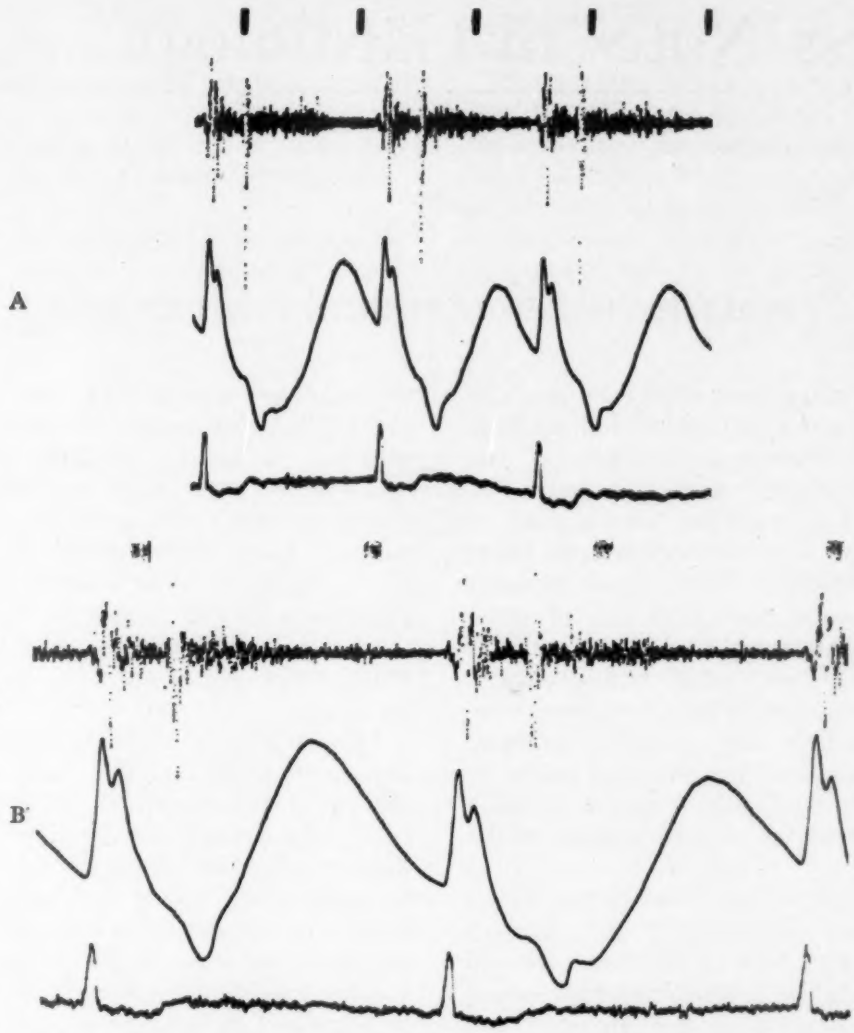

FIG. 1. Above, phonocardiogram at Erb's point (systolic and diastolic murmur). Center, low frequency tracing at apex (rapid systolic and slower diastolic pulsations). Below, electrocardiogram. Time = 0.1 second. A, recorded at 25 mm. per second; B, 50 mm. per second.

in mid-diastole. This second, diastolic impulse was at times higher than the systolic. Its return to the baseline was also slow and occasionally was interrupted by the subsequent apical thrust.

This behavior serves to differentiate the diastolic pulsation from the most common wave of rapid filling, which never overshadows the systolic thrust and which would occur earlier. The condition of aortic insufficiency would cause an even earlier appearance of the phase of rapid filling. Moreover, a singular phenomenon was observed; the diastolic wave was severely affected by respiration and at times completely disappeared.

It was concluded that the diastolic pulsation was caused by the rebound of the aneurysm, a physical sign which was described by Hope over a hundred years ago. Graphic documentation of this phenomenon is rare.

Progress Notes in Cardiology

Edited by EMANUEL GOLDBERGER, M.D., F.A.C.C.

New York, New York

Percutaneous Aortocerebral Angiography

FOR SEVERAL YEARS there have been sporadic reports of various methods of radiographic visualization of individual branches of the aortic arch. However, there are only two previous reports of complete visualization of these vessels plus the cerebral arteries (total cerebral angiography). Both these methods depended on intravenous injections of large amounts of contrast material.

Previous attempts to standardize and simplify aortocerebral angiography have been unsuccessful. Either too little (or too dilute) contrast material was delivered for adequate study or else too strong (and dangerous) a solution would be required for vessels leading to the brain.

Drs. Goffredo G. Gensini and Arthur Ecker (Cardiopulmonary Laboratory, St. Joseph's Hospital, Syracuse, New York) have devised a modification of the Seldinger technic which was especially adapted to the anatomy and hemodynamics of the arch of the aorta and its branches leading to the upper limbs and brain. Their method was based upon the pattern of blood flow in the arch of the aorta as demonstrated by contrast material in (1) radiographs of cases undergoing visualization of the coronary vessels; (2) in glass models; and (3) in cinefluorographic studies of patients suspected of having cerebral arteriosclerosis. The basic features of the method are that it is performed with local anesthesia by percutaneous puncture of the femoral artery for insertion of a plastic catheter. The catheter is advanced under fluoroscopic control to the arch of the aorta. Then the contrast medium is injected while serial radiographs or motion pictures are made.

This method is useful in cases suspected of having aneurysm, stenosis, occlusion, malformation or displacement of the affected vessels. It is useful in studying the rates of blood flow within individual areas of the entire brain. In experienced hands it is safe, reliable and causes the patient little discomfort. A single puncture and single injection results in radiographic visualization of the arch of the aorta, its branches, all the cerebral arteries, cerebral veins and jugular veins.

This method has been done in a series of fifty-four successful injections in eighteen successive clinical cases without mortality or persistent morbidity and with minimal discomfort to the patient.

Suprasternal Thoracic Aortography

DRS. J. STAUFFER LEHMAN, William M. Lemmon, Randal A. Boyer and Edward A. Fitch (Departments of Radiology and Thoracic Surgery, Hahnemann Medical College and Hospital, Philadelphia) describe a method of achieving radiologic opacification of the thoracic aorta employing a needle puncture procedure. The needle is introduced percutaneously in the midline at the base of the neck just above the sternum and then advanced to penetrate the ascending aorta. Further advancement positions the needle tip just above the level of the aortic valve cusps. With the needle so positioned, 30 to 40 cc. of high concentration radiopaque substance is rapidly injected. Emphasis is placed upon contrast electrocardiographic and pressure monitoring during the needle insertion and manipulation.

The principal hazards are inadvertent intramural injection of the radiopaque agent into the aortic wall, and bleeding from the site of aortic needle puncture or needle laceration.

Aortic bleeding evidenced by widening of the superior mediastinum was observed on a number of occasions. Among the 110 attempts at suprasternal thoracic aortography there were thirty-two failures, of which twenty-six were due to inability to effect aortic needle penetration.

The procedure was primarily performed for the following purposes: evaluation for aortic valvular insufficiency, coronary arteriographic studies, and evaluation for patent ductus arteriosus.

The authors describe fifty-three additional cases, including one fatality in the entire series. This fatality was caused by uncontrollable aortic bleeding. They conclude that the hazard of aortic bleeding is sufficiently serious to invalidate any "routine" employment of the suprasternal technic for aortography or coronary arteriography.

Book Reviews

Electrocardiography: Principles and Practice, by Ernest Bloomfield Zeisler. Login Brothers, Chicago, 1960, pp. 374.

Some textbooks on electrocardiography sacrifice validity for oversimplification and promulgate dogmas, errors and misconceptions. Dr. Zeisler attempts instead a more critical consideration of some important problems in electrocardiography. Some of his analyses involve careful study of the original work and full discussion down to minute details. This is a welcome departure even if one is compelled to point out a few serious defects in some of the excellent chapters.

There are a number of diagrams but no illustrations of electrocardiograms. In order to follow many of the author's discussions the reader will have to obtain the original papers.

The author defends the empirical approach. He argues against a resultant vector in the body, the unipolarity of the V leads and the possibility of determining cardiac position from the electrocardiogram. He discusses the limitations in the diagnosis of ventricular hypertrophy and infarction, and he reviews theories of mechanism of the Wolff-Parkinson-White syndrome. He concludes that reciprocal rhythm and retrograde conduction to the atria from ventricular premature systoles occur not at all or only rarely. He presents a classification of heart block with five degrees. He reviews the theories of mechanism of atrial fibrillation and flutter. Spatial vectorcardiography is disposed of in less than a page as a fad with the prediction that it will not prove clinically useful. The chapters on hypertrophy, infarct and Wolff-Parkinson-White syndrome are the best.

The chapter on the physical basis of electrocardiography says nothing about the fascinating and basic new studies with microelectrodes in individual myocardial fibers. The chapter on the normal electrocardiogram is inadequate; ranges of normal are given without data on distribution or frequency of deviations from these values in healthy people. There are limited data for children. The whole question of distinguishing normal in the statistical sense from normal in the sense of healthy, so important in electrocardiography, is barely touched.

The author's discussion of what he believes to be serious errors in other texts is valuable. If his book accomplishes no more than to call attention to prevalent misconceptions about the relation of the electrocardiogram to cardiac position, it will serve a useful purpose. Sometimes one wishes though that he would drop the polemics with other texts to take on more formidable adversaries. The attack on Wilson's concepts is more an attack on what some texts say than a detailed critique of Wilson's and other relevant studies. There is more reference to other texts on the subject of the resultant dipole than to some important recent basic studies.

A principle of least difficulty in the interpretation of the arrhythmias is, according to the author, presented here for the first time. It is the reviewer's impression that something similar to such a principle must have been applied to the analysis of the first clinical and all subsequent arrhythmias. Some readers may question whether the principle has been applied in the author's discussion of reciprocal rhythm, retrograde conduction to the atria from ventricular premature systoles and retrograde conduction in A-V block.

Perhaps the author attempted too much. It may be impossible in 342 pages "to simplify the subject and to make it accessible and useful to the the medical student, the general internist, the cardiologist and the electrocardiographer" and, at the same time, undertake full discussion "with analysis of all the arguments on both sides." Medical students and others with a general interest will probably avoid the book as an introduction to electrocardiography or as a main reference, largely because of the absence of illustrations. More serious students of electrocardiography should find the book provocative and interesting; careful study of the author's arguments alongside the original papers is worth while. ALBERT D. KISTIN, M.D.

Transactions of the American Society for Artificial Internal Organs, vol. 6, edited by George E. Schreiner. Georgetown University Press, Washington, D. C., 1960, pp. 380, $8.00.

This volume deals almost exclusively with artificial organs for the replacement or supplementation of natural functions. It includes a unique collection of semiformal papers presented before a forum of surgeons, internists, physiologists and engineers in April 1960. Not only are the original reports printed in full, with all relevant tables and figures, but the discussions, vivid and sometimes highly informative, have been edited from tape recordings so as to keep the air of spontaneity which characterizes these meetings.

Four sections can be recognized: the first, which concerns external dialysis and experience with the artificial kidney, is probably the most interesting. It demonstrates conspicuous progress in a field that many had come to consider as stagnant. This section includes discussions of concepts and parameters of permeability, descriptions of new technics, such as pulmonary lavage, ultrafiltration of ascites and permanent cannulation for hemodialysis, as well as reports of successful application of the artificial kidney for as long as six months.

The second section deals with heart lung bypass. It seems that the interest for normothermic perfusions has somewhat subsided, because the problems involved in today's applications have been empirically solved. Most contributions are concerned with partial perfusion technics for circulatory assistance, deep hypothermia by blood stream cooling, cardiac metabolism and cardiac arrest.

The section related to implantable artificial organs show a new upsurge of ideas. Valves have been devised which can be made to hold permanently and pumps will soon follow them. The last section covers technicalities of monitoring systems for extracorporeal circulation and design and application of new monitoring devices.

The volume as a whole is a real mine of information for all clinicians and scientists concerned with extracorporeal circulation. Not the least of its merits is the editor's success in making these papers available within three months after their presentation. These transactions embody the most up-to-date information in the field and straight from the horse's mouth, as one might say.

PIERRE M. GALLETTI, M.D., PH.D.

Electrocardiographic Techniques. A Manual for Physicians, Nurses and Technicians, by Kurt Schnitzer. Grune and Stratton, Inc., New York, 2nd Ed., 1960, pp. 109, $4.75.

This handy, little, how-to manual, which has been revised and enlarged, should help its readers to eliminate artefacts and record better electrocardiograms. Simply written, it admirably serves its purpose.

The printing is marred by several typographical errors. For example, the second *e* in *electrocardiographic* has disappeared. Elsewhere, some unaesthetic printing debris detracts from the otherwise attractive type and layout.

RAYMOND HARRIS, M.D.

RECEIVED FOR REVIEW

All books received will be acknowledged in this column. As space permits, books of special interest will receive more extensive reviews.

Verhandlungen der Deutschen-Gesellschaft für Kreislaufforschung. Die Therapie der Herzkrankhieten, by Rudolf Thauer. Dr. Dietrich Steinkopff Verlag, Darmstsdt, 1960, pp. 372.

Quantitative Phonokardiographie. Am Beispiel der respiratorischen und pressorischen Schwankungen der Herztätigkeit, by Paul Heintzen. George Thieme Verlag, Stuttgart, pp. 187, $6.20.

Current Therapy, edited by Howard F. Conn. W. B. Saunders Company, Philadelphia, 1961, pp. 806, $12.50.

These pour le Doctorat en Medecine. Contribution a L'Etude des Ruptures Spontanees des Piliers du Coeur, by Elie S. S. Seroussi. Faculte de Medecine de Paris, 1960, pp. 88.

Index-Handbook of Cardiovascular Agents. Vol. 2 (1951–55). Parts I, II, by Isaac D. Welt, National Academy of Sciences—National Research Council, 1960; Part I, pp. 917; Part II, pp. 649.

Surgical Diseases of the Chest, edited by Brian Blades. C. V. Mosby Company, St. Louis, 1961, pp. 580, $22.00.

Pharmacology. The Nature, Action and Use of Drugs, second edition, by Harry Beckman. W. B. Saunders Company, Philadelphia, 1960, pp. 805, $15.50.

Fetal Electrocardiography. The Electrical Activity of the Fetal Heart, by Saul David Larks, Charles C Thomas, Springfield, 1961, pp. 108, $6.50.

Cardiovascular Dynamics, second edition, by Robert F. Rushmer. W. B. Saunders Company, Philadelphia, 1961, pp. 503.

College News

President's Column

THE COLLEGE HAS a number of different kinds of workshops, but one that appeals to me very much is one that I call "office cardiology." Many years ago while visiting in London, I had the opportunity of spending an afternoon in the office of Dr. William Evans, the distinguished London cardiologist. I learned much watching him handle his office problems and when our College advanced the workshop idea, under the direction of Dr. Joseph B. Wolffe, this type of observation seemed to me to be a good idea for a new kind of workshop.

I have found that the practicing cardiologist is very interested in all the details of the management of a private practice devoted to cardiology. These include methods of history-taking, manner of contact with the patient and how much of that contact may be delegated, the laboratory procedures done routinely, methods of mounting and filing electrocardiograms and even such rather simple things as whether the cardiologist opens his own mail or has his secretary do it.

It is only by the mutual exchange of ideas and close personal relationship that the practice of cardiology can be improved. My hope is that this type of workshop can be extended throughout the country, so that many of our members can profit from it.

By this time you will have all received the program of the New York Annual Meeting. I am particularly pleased that we are able this year not only to have a fine program, but we have been able to have an abstract supplement to the scientific program due to the support by a grant of the Purdue Frederick Company. This is something that I have long thought about and wanted to do, and I think it will add greatly to the success of the Meeting. As you have noted in the program there will be many highlights and I want to mention a few at this time.

Although notice was fairly short, I have been particularly pleased at the wonderful response to the Young Investigators' Award. Twenty-two projects have been submitted. This Award was aided by a grant from the Roche Laboratories.

The opportunity to invite a Guest Lecturer from overseas is a unique privilege for the College and we will be happy to welcome Sir F. Horace Smirk from New Zealand. Geigy Company has given this Lecture its interest and support.

One of my old friends, whom I consider one of the finest speakers in the United States, Dr. Norman Vincent Peale, will address our banquet.

These are only a few of the many interesting events at the Meeting and I look forward to greeting you all in New York.

LOUIS F. BISHOP, M.D.
President

AMERICAN COLLEGE OF CARDIOLOGY

Tenth Annual Meeting

May 17–20, 1961, Biltmore Hotel, New York, New York

Scientific Program

Investigators Session

Wednesday, May 17, 9:00 a.m.–12:00 p.m.

SYMPOSIUM ON
METHODS OF MEASUREMENT OF OXYGEN IN BLOOD

Co-Chairmen: RICHARD GORLIN, M.D., Boston, Mass.
JOHN L. PATTERSON, M.D., Richmond, Va.

1. Introductory Remarks.
   RICHARD GORLIN, M.D., and JOHN L. PATTERSON, M.D.
2. Spectrophotometric Method.
   ABRAHAM M. RANDOLPH, M.D., New York, N. Y.
3. Cuvette Oximetry.
   WM. SUTTERER, M.D., Rochester, Minn. and EARL H. WOOD, M.D., Rochester, Minn.
4. Oxygen Tension by the Bubble Method.
   SOLBERT PERMUTT, M.D., Denver, Colo.

10:40 a.m.—Intermission

5. Polarography: Oxygen Electrode in Vitro.
   GEORGE POLGAR, M.D., Philadelphia, Pa.
6. Polarography: Oxygen Electrode in Vivo.
   SAMI SAID, M.D., Richmond, Va.
7. Gas Chromatography.
   JAY GOODKIND, M.D., New Haven, Conn.

Young Investigators' Award

Wednesday, May 17, 9:00 a.m.–12:00 p.m.

Presentations for the Young Investigators' Award of the American College of Cardiology.

First Scientific Session

Wednesday, May 17, 2:00–5:30 p.m.

Chairman: E. GREY DIMOND, M.D., President Elect.

1. President's Address.
   LOUIS F. BISHOP, M.D., President.
2. A New Method of Estimating Myocardial Blood Flow in Coronary Disease.
   WILLIAM HOLLANDER, M.D., IRVING M. MADOFF, M.D. and ARAM V. CHOBANIAN, Boston, Mass.
3. Measurements of the Total Coronary Blood Flow.
   DAVID W. IRVING, M.D. and ELIOT CORDAY, M.D., Los Angeles, Calif.
4. The Cerebral Circulation in Cardiovascular Disease.
   PAUL NOVACK, M.D., BERNARD GOLUBOFF, M.D., HENRY A. SHENKIN, M.D., FERNANDO A. MENDOZA, M.D., DIEGO DE-ARMAS, M.D., GIAMPIERO BARTOLUCCI, M.D. and AHMED USMAN, M.D., Philadelphia, Pa.
5. Problems in the Use and Evaluation of Measures to Lower Serum Cholesterol.
   MAURICE M. BEST, M.D. and CHARLES H. DUNCAN, M.D., Louisville, Ky.
6. The Practical Significance of the Radioactive Fat Tolerance Test and Its Relation to Current Therapy for Hypercholesterolemia.
   DONALD BERKOWITZ, M.D., JOHN J. SPITZER, M.D. and WILLIAM LIKOFF, M.D., Philadelphia, Pa.

3:30 p.m.—Intermission

Chairman: ROBERT LESLIE, M.D., Vice President.

7. Hypercholesterolemia, A Study in Its Etiology and Why It Is Influenced by Dietary Vegetable Oils.
   WALTER L. EVANS, M.D., WILLIAM B. RAWLS, M.D., CHARLES MISTRETTA, M.D.,

FRANK D'ALESSANDRO, M.D., DIONISIO CALOSA, M.D. and ELIAS TAWIL, M.D., New York, N. Y.

8. Dietary and Lipid Studies in Seventh-Day Adventists.
   RICHARD T. WALDEN, M.D., Loma Linda, Calif., ABRAHAM SUNSHINE, M.D., LOUIS E. SCHAEFER, M.D. and ERNEST WYNDER, M.D., New York, N. Y.
9. The Problem of Hidden Myocardial Infarction.
   STEPHEN R. ELEK, M.D., Los Angeles, Calif.
10. The Use of Steroids in Heart Block.
    MYRON PRINZMETAL, M.D. and REXFORD KENNAMER, M.D., Los Angeles, Calif.
11. Evaluation of Currently Used Agents in the Treatment of Angina Pectoris by Means of the Master Two-Step Test. Peritrate, Cardilate, Isordil, MAO Inhibitors and Mer-29.
    HENRY I. RUSSEK, M.D., Staten Island, N. Y.
12. Long Survival Following Myocardial Infarction. Report on 255 Patients Living Ten Years or Longer After the First Attack.
    LOUIS H. SIGLER, M.D., Brooklyn, N. Y.

Fireside Conferences

Wednesday, May 17, 8:30–10:30 p.m.

1. Arrhythmias and Their Management.
   SAMUEL BELLET, M.D., Moderator, Philadelphia, Pa., SIMON DACK, M.D., New York, N. Y. and GORDON K. MOE, M.D. Utica, N. Y.
2. The Present Status of Fibrinolysins in Practice.
   EUGENE E. CLIFFTON, M.D., Moderator, New York, N. Y., JULIAN AMBRUSE, M.D., Buffalo, N. Y., KENNETH M. MOSER, M.D., Washington, D. C. and IRWIN NYDICK, New York, N. Y.
3. The Management of Angina Pectoris.
   ELIOT CORDAY, M.D., Moderator, Los Angeles, Calif., FRANCIS CHAMBERLAIN, M.D., San Francisco, Calif., and RICHARD S. COSBY, M.D., Pasadena, Calif.
4. The Surgical Management of Extracranial Arterial Occlusive Disease.
   MICHAEL E. DEBAKEY, M.D., Houston, Texas and MILLER FISHER, M.D., Boston, Mass.
5. Problems in Vector-Electrocardiography.
   STEPHEN R. ELEK, M.D., Co-moderator, Los Angeles, Calif., ARTHUR GRISHMAN, M.D., Co-moderator, New York, N. Y., JOHN A. OSBORNE, M.D., Vancouver, B. C. and THOMAS J. WALSH, M.D., St. Louis, Mo.
6. Anticoagulant Therapy in Thrombo-Embolic Disease States.
   WILLIAM T. FOLEY, M.D., Moderator, New York, N. Y., E. STERLING NICHOL, M.D., Miami, Fla. and BENJAMIN MANCHESTER, M.D., Washington, D. C.
7. Advantages and Disadvantages in the Surgical Treatment of Coronary ArteryDisease.
   DWIGHT E. HARKEN, M.D., Moderator, Boston, Mass., RICHARD GORLIN, M.D., Boston, Mass., WILLIAM LIKOFF, M.D., Philadelphia, Pa. and F. MASON SONES, JR., M.D., Cleveland, Ohio.
8. Problems in Electrocardiography.
   IRWIN HOFFMAN, M.D., Moderator, Los Angeles, Calif., J. RODERICK KITCHELL, M.D., Philadelphia, Pa. and JOSEPH E. F. RISEMAN, M.D., Boston, Mass.
9. Problems in Cardiovascular Roentgenology.
   GEORGE JACOBSON, M.D., Moderator, Los Angeles, Calif., JOHN A. EVANS, M.D., New York, N. Y., MELVIN M. FIGLEY, M.D., Seattle, Wash. and JOHN KIRKPATRICK, JR., M.D., Philadelphia, Pa.
10. Practical Problems in Open Heart Surgery and the Surgical Treatment of Acquired and Congenital Heart Lesions Using Open Technics.
    JEROME H. KAY, M.D., Moderator, Los Angeles, Calif., ROBERT GROSS, M.D., Boston, Mass. and CHARLES P. BAILEY, M.D., New York, N. Y.
11. Recognition and Management of Congenital Defects in the First Year of Life.
    JOHN D. KEITH, M.D., Moderator, Toronto, Ontario, J. FRANK DAMMANN, JR., M.D., Charlottesville, Va., MARY ALLEN ENGLE, M.D., New York, N. Y., EDWARD C. LAMBERT, M.D., Buffalo, N. Y., JAMES MANNING, M.D., Rochester, N. Y., ALEXANDER S. NADAS, M.D., Boston, Mass. and P. A. ONGLEY, M.D., Rochester, Minn.
12. Problems in Electrocardiography.
    E. LEPESCHKIN, M.D., Moderator, Burlington, Vt., ARTHUR M. MASTER, M.D., New York, N. Y., DAVID SCHERF, M.D., New York, N. Y. and ROBERT F. ZIEGLER, M.D., Detroit Mich.
13. The Evaluation of the Rheumatic Fever Suspect.
    BENEDICT F. MASSELL, M.D., Moderator, Boston, Mass., EDWARD E. FISCHEL, M.D.,

New York, N. Y., MILTON SASLAW, M.D., Miami, Fla. and JACK A. SHEINKOPF, M.D., Beverly Hills, Calif.

14. The Edematous States, Their Management.
JOHN H. MOYER, M.D., Moderator, Philadelphia, Pa., ALBERT BREST, M.D., Philadelphia, Pa., RAY W. GIFFORD, JR., M.D., Rochester, Minn. and SIR F. HORACE SMIRK, M.D., Dunedin, New Zealand.

15. Monoamine Oxidase Inhibitors.
ROBERT W. OBLATH, M.D., Moderator, Sherman Oaks, Calif., WILLIAM HOLLANDER, M.D., Boston, Mass., HENRY I. RUSSEK, M.D., Staten Island, N. Y., ARTHUR L. SCHERBEL, M.D., Cleveland, Ohio and GERHARD ZBINDEN, M.D., Nutley, N. J.

16. The Role of the Catecholamines in Cardiovascular Diseases.
WILHELM RAAB, M.D., Moderator, Burlington, Vt., J. E. SZACKAS, M.D., Bethesda, Md., A. C. WIGMAN, M.D., Detroit, Mich., MORTON D. BOGDONOFF, M.D., Durham, N. C. and ALBERT J. PLUMMER, M.D., Summit, N. J.

17. Does Stress Play a Role in Atherogenesis?
RAY H. ROSENMAN, M.D., Moderator, San Francisco, Calif., CHESTERFIELD G. GUNN, M.D., Oklahoma City, Okla. and REUBEN STRAUS, M.D., Burbank, Calif.

18. The Problems in Digitalis Administration.
JOHN J. SAMPSON, M.D., Moderator, San Francisco, Calif., CHARLES K. FRIEDBERG, M.D., New York, N. Y. and BERNARD LOWN, M.D., Boston, Mass.

19. Adaptation of Cardiovascular Function to Hot and Cold Environments.
KARL E. SCHAEFER, M.D., Moderator, New London, Conn., DAVID E. BASS, M.D., Natick, Mass., AUSTIN HENSCHEL, M.D., Natick, Mass., THOMAS F. HORNBEIN, M.D., St. Louis, Mo. and DUANE E. GRAVELINE, M.D., Wright-Patterson AFB, Ohio.

20. Serum Triglyceride Levels in Man in Health and Disease.
LOUIS E. SCHAEFER, M.D., Moderator, New York, N. Y., JULES HIRSCH, M.D., New York, N. Y. and KURT HIRSCHHORN, M.D., New York, N. Y.

21. Congenital Defects Involving the Great Vessels.
HELEN B. TAUSSIG, M.D., Baltimore, Md. and DENTON A. COOLEY, M.D., Houston, Texas.

22. Peripheral Vascular Problems.
TRAVIS WINSOR, M.D., Moderator, Los Angeles, Calif., DAVID ABRAMSON, M.D., Chicago, Ill. and CHESTER HYMAN, M.D., Los Angeles, Calif.

23. The Management of Cerebral Vascular Disease.
IRVING S. WRIGHT, M.D., Moderator, New York, N. Y., SIGMUND GROCH, M.D., New York, N. Y. and ROBERT G. SIEKERT, M.D., Rochester, Minn.

24. Hypothermia.
W. GLENN YOUNG, JR., M.D., Moderator, Durham, N. C., WALTER L. FLOYD, M.D., Durham, N. C., ARCHER S. GORDON, M.D., Los Angeles, Calif. and JOHN Y. TEMPLETON, III, M.D., Philadelphia, Pa.

25. Mechanisms of Syncope.
WILLARD J. ZINN, M.D., Moderator, Los Angeles, Calif., GEORGE DERMSKIAN, M.D., New York, N. Y., WILLIAM C. GIBSON, M.D., Vancouver, B. C., ROGER B. HICKLER, M.D., Boston, Mass. and JOHN B. SCHWEDEL, M.D., New York, N. Y.

Second Scientific Session

Thursday, May 18, 9:00–11:30 a.m.

SYMPOSIUM ON AORTIC VALVE

Chairman: CHARLES A. HUFNAGEL, M.D., Washington, D. C.

1. Congenital Bicuspid Aortic Valve. The Natural History of Nine Cases.
MATTHEW J. FERGUSON, M.D. and Sister MICHAEL MARIE O'BRIEN, M.D., New York, N. Y.

2. A Critical Review of Aortic Stenosis.
RICHARD S. COSBY, M.D., BALAKRISHA HEGDE, M.D. and MARY MAYO, M.D., Los Angeles, Calif.

3. The Surgical Problems of Congenital Aortic Stenosis.
BERT W. MEYER, M.D., Los Angeles, Calif.

4. Experimental and Clinical Experiences with the Bicuspid Operation for Aortic Insufficiency.
JOSEPH J. GARANELLA, M.D., W. ROBERT SCHMIDT, M.D. and NATHAN KENNETH JENSON, M.D., Minneapolis, Minn.

5. The Surgical Treatment of Aortic Regurgitation by Valvular Prostheses.
EARLE B. KAY, M.D., DAVID MENDELSOHN, M.D. and HENRY A. ZIMMERMAN, M.D., Cleveland, Ohio.

10:30 a.m.—Intermission

6. Partial and Complete Aortic and Mitral Valve Prostheses.
   DWIGHT E. HARKEN, M.D., WARREN J. TAYLOR, M.D., ARMAND A. LEFEMINE, M.D., STEVEN LUNZER, M.D., HENRY B. C. LOW, M.D., MANFRED L. COHEN, M.D. and ANNA M. FOSBERG, M.D., Boston, Mass.
7. Open Heart Treatment of Mitral Insufficiency and Combined Mitral Stenosis and Insufficiency.
   JEROME H. KAY, M.D. and OSCAR MAGIDSON, M.D., Los Angeles, Calif.
8. Reconstructive Methods for Aortic Valvular Disease.
   CHARLES A. HUFNAGEL, M.D., PETER W. CONRAD, M.D., ROQUE PIFARRE, M.D. and NESTER DEVENECIA, M.D., Washington, D. C.

Panel Discussion by All Essayists

Third Scientific Session

Thursday, May 18, 11:30 a.m.–12:30 p.m., 2:00–4:30 p.m.

SYMPOSIUM ON HYPERTENSION

Chairman: JOHN H. MOYER, M.D., Philadelphia, Pa.

CONVENTION GUEST LECTURE

Introduction: GEORGE C. GRIFFITH, M.D.
Some Principles of Hypotensive Therapy Considered in Relationship to the Pathogenesis of Essential Hypertension.
SIR F. HORACE SMIRK, M.D., F.R.C.P., Dunedin, New Zealand.

12:30 p.m.—Intermission

1. Mechanisms in Essential Hypertension.
   MILTON MENDLOWITZ, M.D., STANLEY E. GITLOW, M.D., ROBERT L. WOLF, M.D. and NOSRAT NAFTCHI, M.D., New York, N. Y.
2. Pharmacodynamics and Clinical Use of Three Drugs Which Block Sympathetic Neural Activity.
   WALTER M. KIRKENDALL, M.D., Iowa City, Iowa.
3. Decarboxylase Inhibitors in the Treatment of Hypertension.
   ALBERT BREST, M.D., Philadelphia, Pa.
4. Reversible Renal Hypertension. Clinical Characteristics and Predictive Tests.
   MORTON H. MAXWELL, M.D., Los Angeles, Calif.
5. Pheochromocytoma.
   VARNER J. JOHNS, JR., M.D., Los Angeles, Calif.
6. Flexibility in Drug Treatment of Essential Hypertension.
   ROBERT W. WILKINS, M.D., Boston, Mass.
7. The Isotope Renogram, Differential Renal-Function Study and Aorto-Renal Arteriogram in the Clinical Evaluation of Hypertensive Patients.
   RAY W. GIFFORD, JR., M.D., and JAMES C. HUNT, M.D., Rochester, Minn.
8. Diagnosis and Treatment of Renovascular Hypertension.
   GEORGE C. MORRIS, JR., M.D., Houston, Texas.

Panel Discussion by All Essayists

Annual Business Meeting

Thursday, May 18, 4:30–5:30 p.m.

Fourth Scientific Session

Friday, May 19, 9:00 a.m.–12:30 p.m.

SYMPOSIUM ON
THE EVALUATION OF FIBRINOLYTIC AGENTS IN THE TREATMENT OF CARDIOVASCULAR DISEASE

Chairman: JOHN S. LA DUE, M.D., Secretary

1. Studies in Experimental Myocardial Infarction.
   PAUL RUEGSEGGER, M.D., New York, N. Y.
2. Technics of Treatment.
   ALAN JOHNSON, M.D., New York, N. Y.
3. Experiences in Peripheral Vascular Disease.
   EUGENE E. CLIFFTON, M.D., New York, N. Y.
4. Clinical Evaluation in Acute Myocardial Infarction.
   ISAAC H. RICHTER, M.D., New York, N. Y.

Panel Discussion

10:30–11:00 a.m.—Intermission

Chairman: C. WALTON LILLEHEI, M.D., Vice President

5. Cardiac Metabolism.
   RICHARD J. BING, M.D., Detroit, Mich.
6. New Methods and Technics in Cardiovascular Roentgenology.
   GEORGE JACOBSON, M.D., Moderator, Los Angeles, Calif., JOHN A. EVANS, M.D., New York, N. Y., MELVIN M. FIGLEY, M.D., Seattle, Wash. and JOHN KIRKPATRICK, JR., M.D., Philadelphia, Pa.

Fifth Scientific Session

Friday, May 19, 2:00–5:30 p.m.

Chairman: IRVING BROTMAN, M.D., Assistant Secretary

1. The Hydrogen-Platinum Electrode System in Detection of Cardiac Shunts.
   EDWARD S. HYMAN, M.D., ALBERT L. HYMAN, M.D., KENNETH HYATT, M.D. and

William Myers, M.D., New Orleans La.

2. Observations on the Use of Externally Monitored Radioisotopes in Measuring Coronary Blood Flow.
   Sylvan L. Weinberg, M.D., G. Richard Grove, M.D., Cemal M. Cagirgan, M.D. and Warren Blanchard, M.D., Dayton, Ohio.
3. Assisted Circulation in Acute Coronary Occlusion. I. Production of Acute Myocardial Infarction with Graded Doses of Plastic Microspheres.
   John A. Jacoby, M.D., Warren J. Taylor, M.D., George T. Smith, M.D., Richard Gorlin, M.D. and Dwight E. Harken, M.D., Boston, Mass.
4. Prolonged Mechanical Assistance in Left-Sided Heart Failure.
   Charles P. Bailey, M.D., Robert A. O'Connor, M.D., Abraham Schaffer, M.D., Teruo Hirose, M.D. and Photos Panagopoulos, M.D., New York, N. Y.
5. Timing of Vibrocardiographic Wave Intervals to Detect Coronary Insufficiency.
   Clarence M. Agress, M.D., Stanley Wegner, M.D. and Robert M. Muller, M.D., Los Angeles, Calif.
6. High Frequency Phonocardiography.
   Aldo A. Luisada, M.D. and Giuliano di Bartolo, M.D., Chicago, Ill.

3:30 p.m.—Intermission

7. The Role of Intracardiac Phonocardiography in the Differential Diagnosis of Continuous Precordial Murmurs.
   Howard F. Warner, M.D., Abdol-Nabi Moghadam, M.D., Jerome A. Hubsher, M.D., John D. Wallace, M.D. and David H. Lewis, M.D., Philadelphia, Pa.
8. Direct Studies of the Activation of the Purkinje System Before and After Left Bundle Branch Block.
   Robert S. Venerose, M.D., Jackson H. Stuckey, M.D., Brian F. Hoffman, M.D. and Martin Seidenstein, M.D., Brooklyn, N. Y.
9. Myocardial Hypoxia Elicited by Neurogenic and Blood-borne Catecholamines During Impairment of Coronary Dilatability.
   Wilhelm Raab, M.D., E. Lepeschkin, M.D., Paul van Lith, M.D. and H. C. Herrlich, M.D., Burlington, Vt.
10. The Relationship Between Coronary Blood Flow, Myocardial Oxygen Consumption and Cardiac Work as Influenced by Pharmacologic Agents.
    Vernon E. Wendt, M.D., John F. Sundermeyer, M.D., P. B. den Bakker, M.D. and Richard J. Bing, M.D., Detroit, Mich.
11. The Hemodynamic Effects of Prolonged Hypothermia Combined with Closed-Chest Extracorporeal Circulation in Experimental Myocardial Infarction with Shock.
    Leslie A. Kuhn, M.D., Frank M. Weiser, M.D., A. Robert Beck, M.D., John D'Aria, M.D. and Irwin Krasna, M.D., New York, N. Y.
12. Treatment of Heart Block and Adams-Stokes Syndrome With Oral Sustained-Action Isoproterenol.
    Simon Dack, M.D. and Stanley R. Robbin, M.D., New York, N. Y.

Groedel Memorial Lecture on Humanities in Medicine

Friday evening, May 19, 8:00 p.m.

The Medical and Scientific Significance of the Seemingly Small, Trivial and Insignificant.

William B. Bean, M.D., Iowa City, Iowa.

Sixth Scientific Session

Saturday, May 20, 9:00 a.m.–12:30 p.m.

Chairman: Aldo A. Luisada, M.D., Trustee.

1. Physiologic Aspects of Hemangioblastic Tissues.
   Simon Rodbard, M.D. and Barbara Howell, M.D., Buffalo, N. Y.
2. The Role of Isopropylnorepinephrine in the Treatment of Digitalis Intoxication.
   David J. Baker, M.D., Paul M. Nonkin, M.D., Martin S. Sternberg, M.D. and Fred Wasserman, M.D., Coral Gables, Fla.
3. The Combined Use of Dihydroergocornine Methane Sulphonate (DHO-180) and Phenylindandione (Hedulin) in the Treatment of Acute Cerebral Thrombosis. A Preliminary Study.
   Ralph M. Tandowsky, M.D., Hollywood, Calif.
4. Sodium D-Thyroxine in the Therapy of Hypercholesterolemia of Coronary Artery Disease.
   Sheldon R. Bender, M.D., Philadelphia, Pa.
5. The Rib Syndrome.
   Maurice S. Rawlings, M.D., Chattanooga, Tenn.

6. The Use of Long Term Anticoagulant Therapy in Private Practice for Coronary Heart Disease.
   W. T. McCollum, M.D., Kent Alexander, M.D., Arthur E. Schmidt, M.D., Gerald Honick, M.D. and Leo Wade, M.D., Oklahoma City, Okla.

10:30 a.m.—Intermission

Chairman: I. Frank Tullis, M.D., Trustee

7. Causes of Pulmonary Artery Stenosis—Intra- and Extra-Luminal.
   David C. Levinson, M.D. and Ronald Danzig, M.D., Los Angeles, Calif.
8. Aortico-Pulmonary Septal Defect.
   Henry N. Neufeld, M.D., Richard G. Lester, M.D., Ray C. Anderson, M.D., Paul Adams, Jr., M.D., C. Walton Lillehei, M.D. and Jesse E. Edwards, M.D., Minneapolis, Minn.
9. The Differential Diagnosis of Patent Ductus Arteriosus and Ventricular Septal Defect in Infancy.
   Abdol-Nabi Moghadam, M.D., Jerome A. Hubsher, M.D., Howard F. Warner, M.D., John D. Wallace, M.D. and David H. Lewis, M.D., Philadelphia, Pa.
10. Patent Ductus Arteriosus as a Cause of Congestive Heart Failure in the First Year of Life.
    Martin J. Frank, M.D., John D. McGinty, M.D., Timothy J. Regan, M.D., Prescott Jordan, Jr., M.D. and Harper K. Hellems, M.D., Jersey City, N. J. and Detroit, Mich.
11. Acute Effects of Triparanol Therapy.
    David H. Blankenhorn, M.D. and Oliver T. Kuzma, M.D., Los Angeles, Calif.
12. Urine Glutamic Oxalacetic Transaminase Activity in Acute Myocardial Infarction.
    Robert B. Kalmansohn, M.D. and Richard W. Kalmansohn, M.D., Los Angeles, Calif.
13. Alterations of Indices of Liver Function in Congestive Heart Failure with Particular Reference to Serum Enzymes.
    Sidney M. Richman, M.D., Abner Delman, M.D. and David Grob, M.D., Brooklyn, N. Y.

Regional Meeting
Area of Massachusetts

April 18, 1961 at 8 P.M.

Peter Bent Brigham Hospital, Boston, Mass.

Topic: Aortic Valve Reconstructions—Present Status

Speakers: Charles A. Hufnagel, M.D.
J. Gordon Scannell, M.D.
Ralph A. Deterling, Jr., M.D.
Dwight E. Harken, M.D.

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1. Riseman, J.E.F., *et al.*: Circulation *17*:22 (Jan.) 1958.

2. Russek, H.I.: Circulation *18*:774 (Oct.) 1958.

3. Hirshleifer, I., *et al.*: Scientific Exhibit, A.M.A., Atlantic City, N. J., June, 1959.

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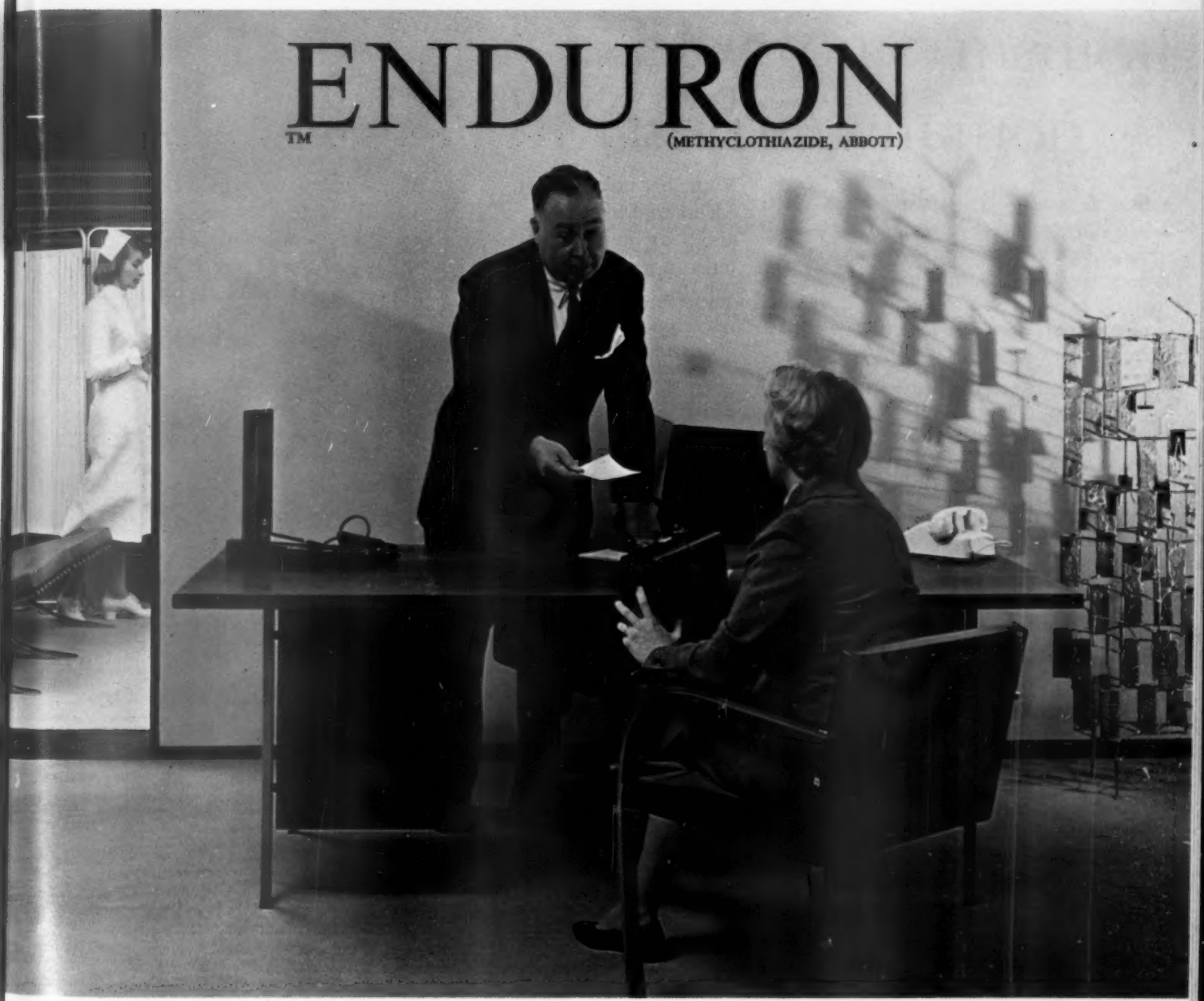

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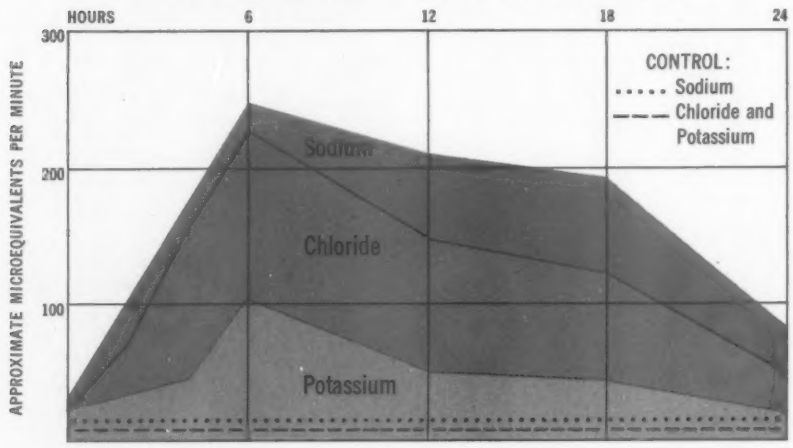

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1. Ford, R. V., Current Therap. Res., 2:422-430, Sept., 1960.
2. Bryant, J. M., et. al., Current Therap. Res., 3:1-4, Jan., 1961.

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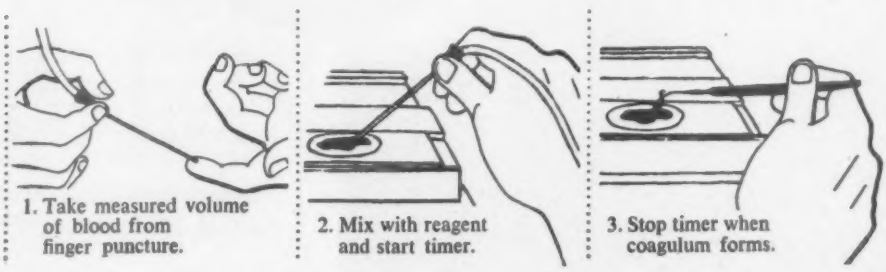

1. Take measured volume of blood from finger puncture.
2. Mix with reagent and start timer.
3. Stop timer when coagulum forms.

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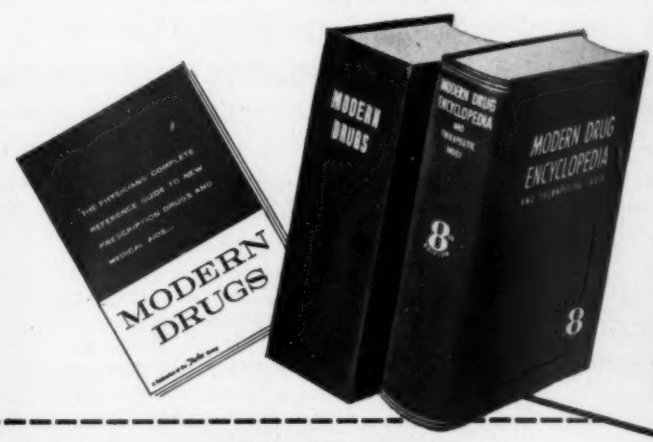

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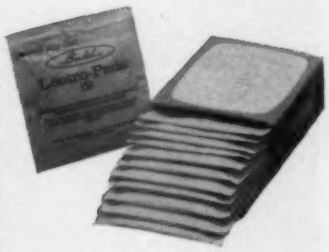

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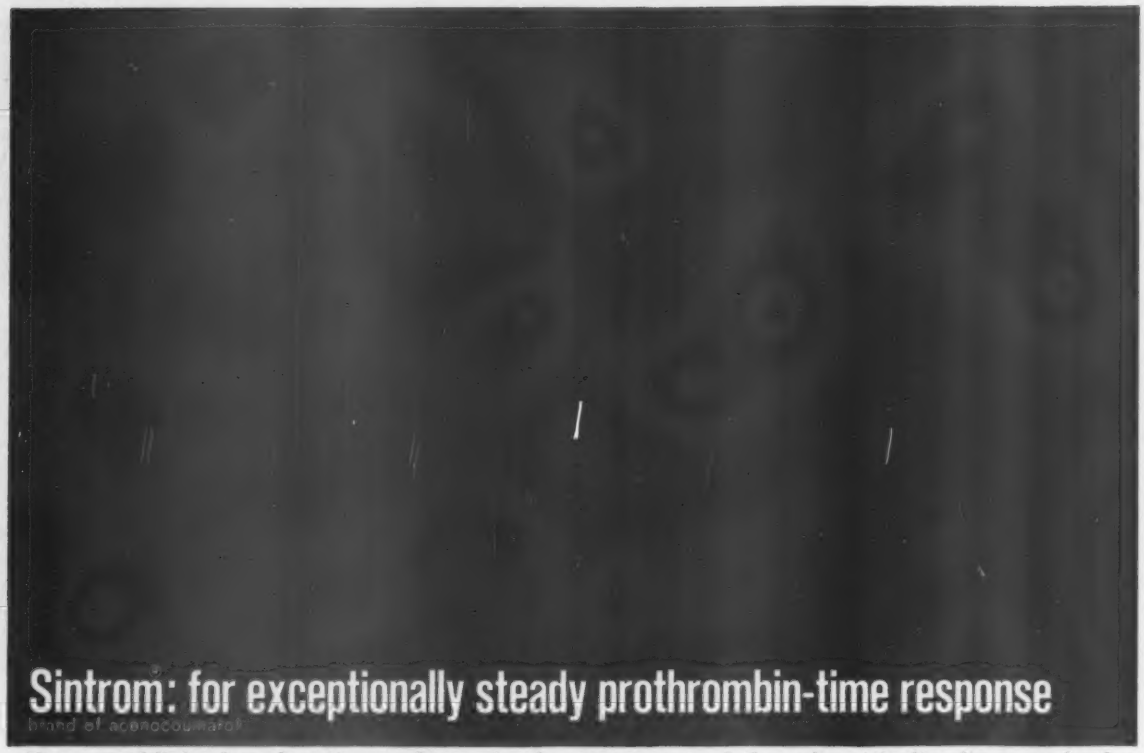

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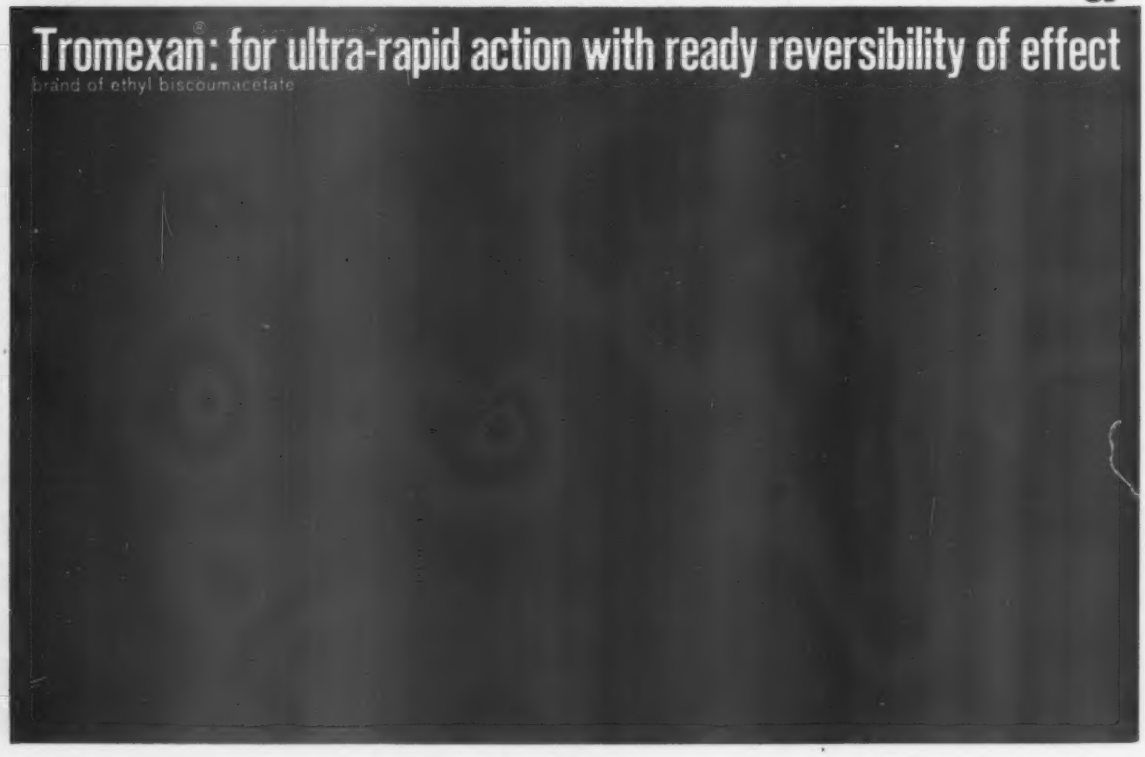

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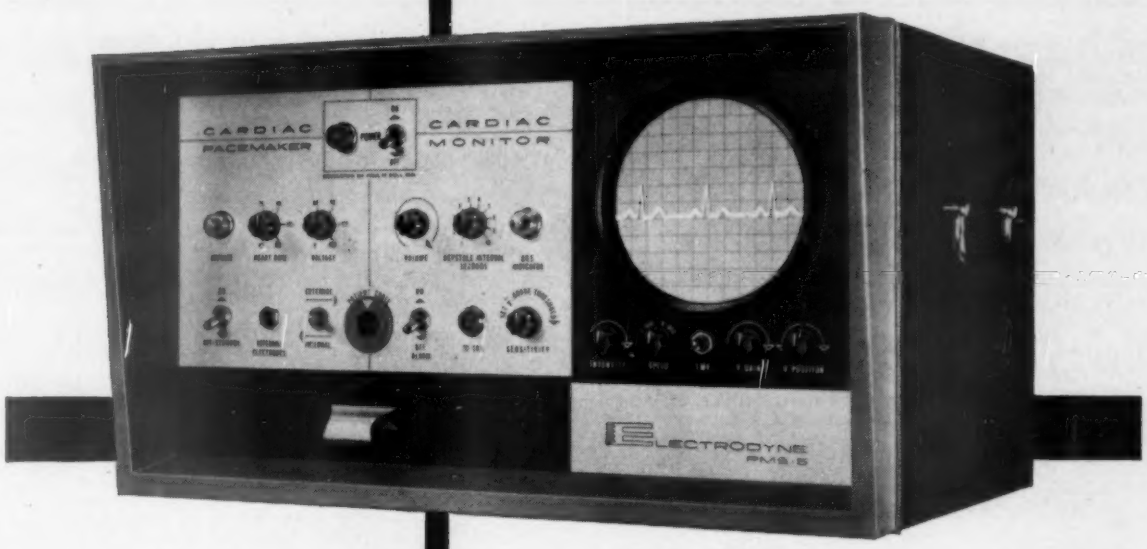

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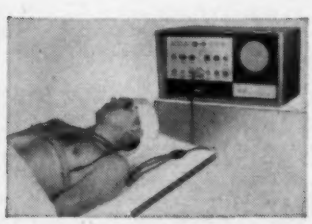

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Vitamin A	25,000 U.S.P. Units
Vitamin D	1,000 U.S.P. Units
Thiamine Mononitrate	10 mg.
Riboflavin	10 mg.
Niacinamide	100 mg.
Vitamin C	200 mg.
Pyridoxine Hydrochloride	5 mg.
Calcium Pantothenate	20 mg.
Vitamin B_{12}	5 mcg.

For full information see your Squibb Product Reference or Product Brief.

1. Youmans, J. B.: Am. J. Med. **25**:659 (Nov.) 1958.
2. Kampmeier, R. H.: Am. J. Med. **25**:662 (Nov.) 1958.

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ways PICKER NUCLEAR can help you...

dual detection

renal function
hepatic function
cardiac output
circulation time
cerebral blood flow
cardiac shunt

for separate counting
of radioactivity
from paired organs
or two points
in a flow system

Picker Nuclear can help you study hypertension of renal origin, or acute obstruction or nephrosis of one or both kidneys by means of a dual detection system. The tests require no catheterization; provide information about each kidney independently. Reliability is enhanced because the detectors can be placed and held in position with great accuracy, and because their shielding minimizes cross interference.

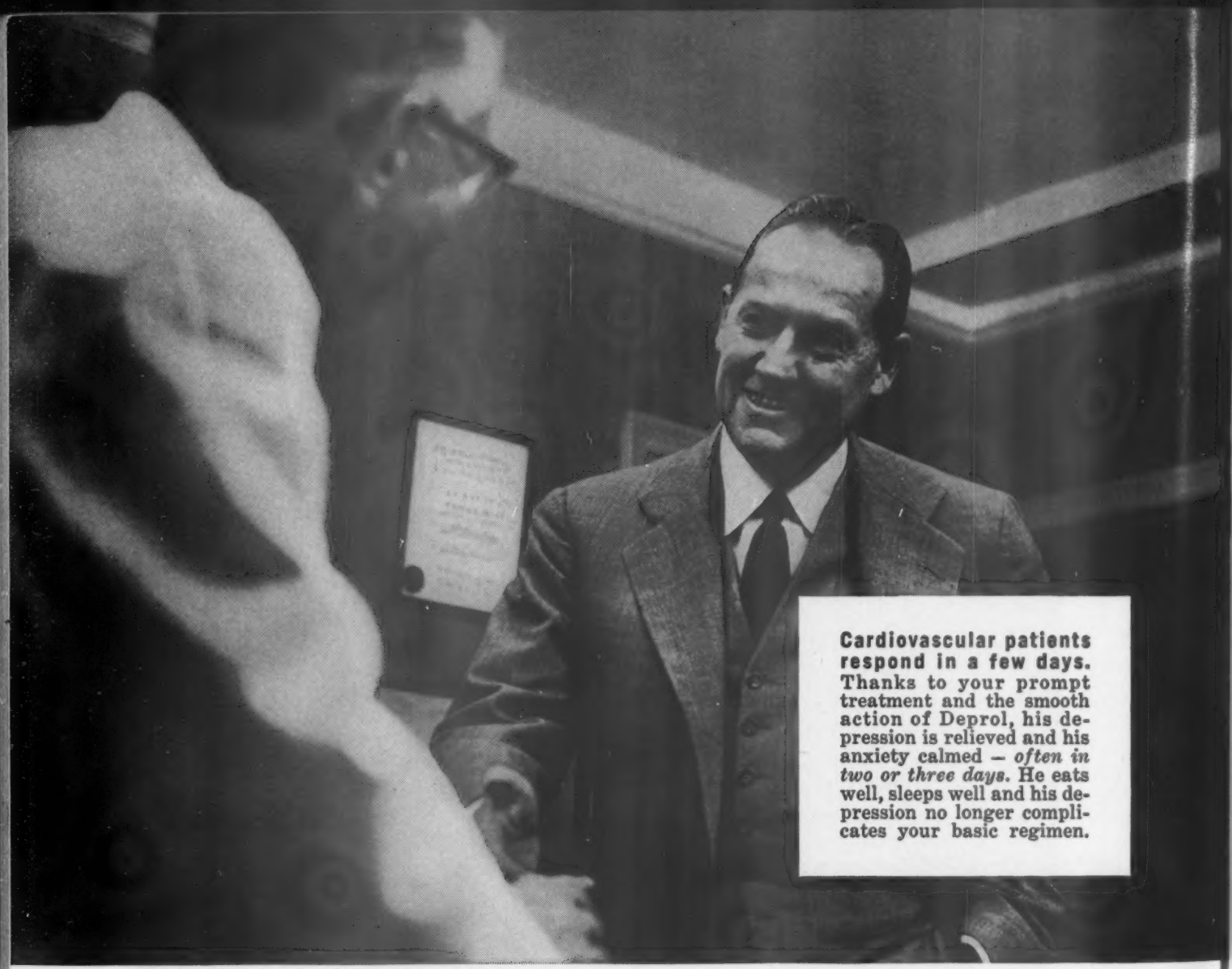
The twin mast mobile carriage mounts the detectors so flexibly that they may be aimed independently at a lying or sitting patient at any angle, from above or below, separated by several feet, or snugged side by side. Such wide-ranging movements make for rapid easy placement of probes for testing widely separated points in a flow system: e.g. circulation time, cardiac output, and similar investigations.

This Dual Detection system is one of the comprehensive Picker line of nuclear instrumentation and supplies: all marketed and serviced through a national network of company offices staffed by trained Picker people. (Picker alone in the nuclear field offers this caliber of local service).

For details call your district office (see 'phone book) or write Picker X-Ray Corporation, 25 South Broadway, White Plains, New York.

Picker nuclear

The dual detection system in use for renal function study. It employs two detectors, a dual ratemeter, a dual recorder, and (optionally) two pulse height analyzers, all "packaged" in a sturdy mobile support.



Cardiovascular patients respond in a few days. Thanks to your prompt treatment and the smooth action of Deprol, his depression is relieved and his anxiety calmed – *often in two or three days.* He eats well, sleeps well and his depression no longer complicates your basic regimen.

Lifts depression...as it calms anxiety!

For cardiovascular patients–a smooth, balanced action that lifts depression as it calms anxiety...rapidly and safely

Balances the mood–no "seesaw" effect of amphetamine-barbiturates and energizers. While amphetamines and energizers may stimulate the patient – *they often aggravate anxiety and tension.* And although amphetamine-barbiturate combinations may counteract excessive stimulation – *they often deepen depression.*

In contrast to such "seesaw" effects, Deprol lifts depression as it calms anxiety – both at the same time.

Acts swiftly–the patient often feels better, sleeps better, within two or three days. Unlike most other antidepressant drugs, Deprol relieves the patient quickly – often within two or three days.

Acts safely – no danger of hypotension. Deprol does not cause hypotension, tachycardia, jitteriness, or liver toxicity. It can be safely administered with basic cardiovascular therapy.

Dosage: Usual starting dose is 1 tablet q.i.d. When necessary, this may be gradually increased up to 3 tablets q.i.d.
Composition: 1 mg. 2-diethylaminoethyl benzilate hydrochloride (benactyzine HCl) and 400 mg. meprobamate.
Supplied: Bottles of 50 light-pink, scored tablets. Write for literature and samples.

▲Deprol▲

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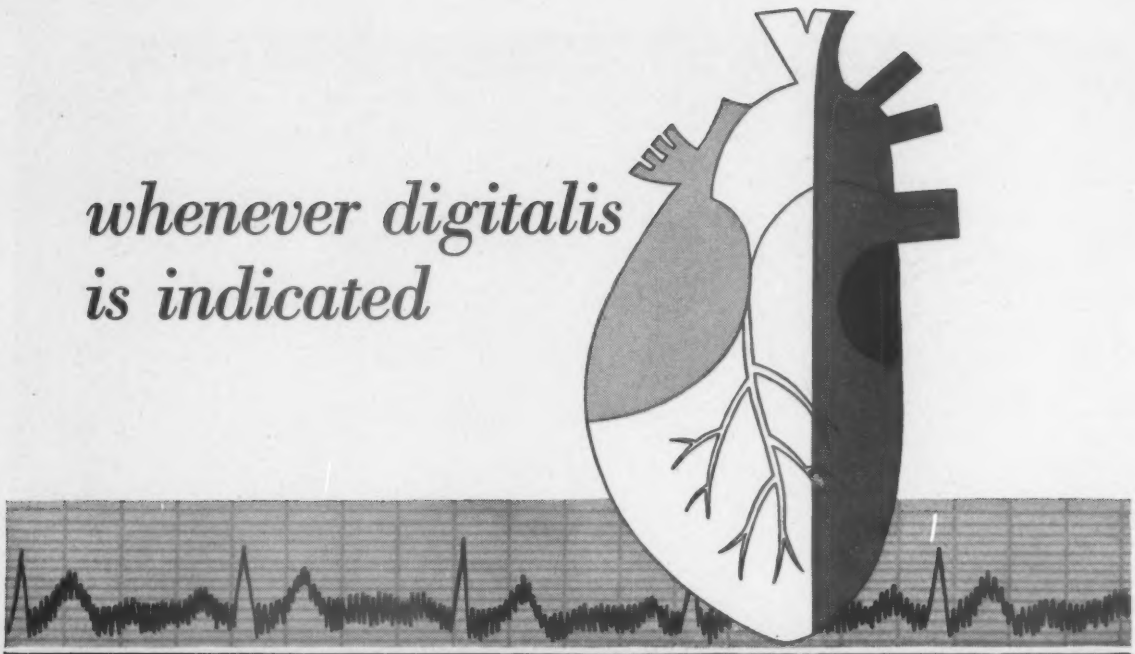

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Lown, B., and Levine, S. A.: Current Concepts in Digitalis Therapy, Boston, Little, Brown & Company, 1954, p. 23, par. 2.

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0.5 mg. in 2 cc. (I.M. or I.V.)

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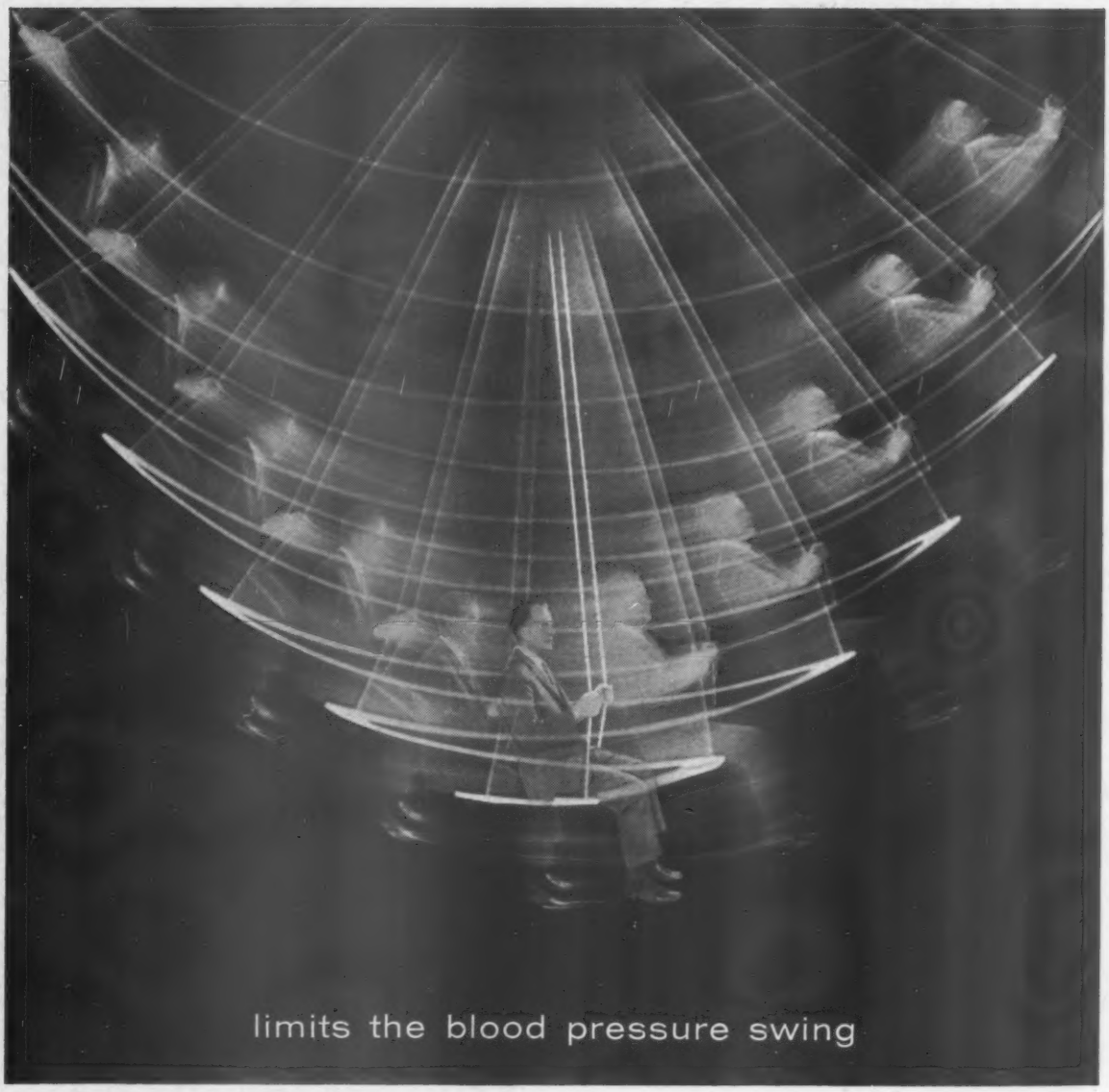

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Rautrax-N*

Squibb Standardized Whole Root Rauwolfia Serpentina (Raudixin) and Bendroflumethiazide (*Naturetin) with Potassium Chloride

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'RAUDIXIN'®, 'RAUTRAX'® AND 'NATURETIN'® ARE SQUIBB TRADEMARKS.

If postcoronary management is
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"In a controlled clinical study of 260 postcoronary patients, one-half were given sublingual heparin and one-half received conventional treatment. During the period of observation, averaging more than 2 years per patient, there were 12 recurrent infarctions in the heparin-treated group and 38 in the control group. This difference is statistically significant."

Fuller, H. L.: Angiology *11*:200 (June) 1960.

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*Registered trade mark. Patent applied for.

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1. California Med. *91*:327 (Dec.) 1959.
2. Clin. Res. 7:388, 1959.

Riker Northridge, California